The Non-Invasive Application of Electrocardiography in the Optimization of Cardiac Resynchronization Therapy

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DEDICATION

This dissertation is dedicated to my grandfather, Adie Daniel Harbin, Jr.

ABSTRACT

Cardiac resynchronization therapy (CRT) is intended to reverse electrical dyssynchrony and improve systolic function in heart failure patients. However, roughly 30% of recipients do not clinically or echocardiography benefit, despite advancements with implant techniques and pacing technology, and are considered to be non-responders (Auricchio & Prinzen, 2011). Suboptimal postoperative device programming of the interventricular and atrioventricular delays, and the left ventricular (LV) pacing vector in quadripolar leads, is thought to be a prevailing cause of this persistent non-response (Mullens et al., 2009). Device optimization of pacing configurations is highly underutilized, and research has yet to establish a standardized, patient-specific methodology that can be routinely used in outpatient heart failure clinics (Gras, Gupta, Boulogne, Guzzo, & Abraham, 2009; N. Varma et al., 2019). The use of electrocardiography in device optimization is supported by the notion that synchronous ventricular electrical activation is a requisite for adequate systolic and diastolic function (Nguyen, Verzaal, van Nieuwenhoven, Vernooy, & Prinzen, 2018). Electrocardiography has furthermore shown promise in routine CRT device optimization owning to its non-invasive, inexpensive, and practical attributes. QRS duration shortening during the paced rhythm, as well as metrics of wavefront fusion and cancellation, on 12-lead electrocardiograms have been reported to correlate with subsequent LV reverse remodeling (Gage et al., 2018; Sweeney et al., 2014; Sweeney et al., 2010). Innovations in technology allow for the application of multiple unipolar electrodes placed over the upper anterior and posterior torso (Bank et al., 2018; Johnson et al., 2017; Rickard et al., 2020). The intent of this technology, as depicted in its ability to simultaneously acquire ventricular activation from both anterior and posterior surfaces, is to provide a better assessment of electrical dyssynchrony relative to that of a 12-lead electrocardiogram. Previous reports have shown that this technology can accurately, non-invasively, and efficiently measure electrical heterogeneity in patients with CRT devices (Gage et al., 2017). The purpose of this dissertation is to use this technology to: (1) quantify how a device-based pacing algorithm improves electrical resynchronization, and (2) evaluate the therapeutic window on the corresponding potential of electrical resynchronization during left ventricular unipolar pacing.

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CHAPTER 1. INTRODUCTION

Since Bakken and Lillehei invented the first wearable cardiac pacemaker at the University of Minnesota in 1957, advancements in pacing technology and the addition of a left ventricular (LV) lead integrated with a traditional dual-chamber pacemaker gave rise to the development of cardiac resynchronization therapy (CRT) (Steinhaus, 2008). Otherwise referred to as atrial-synchronized biventricular pacing, CRT involves a transvenous generator implant with three pacing leads, allowing for the ability to pace and sense both ventricular chambers with respect to an intrinsic, or paced, right atrial depolarization. Initially approved by the Food and Drug Administration in 2001, multiple randomized clinical trials in over 10,000 patients have since established the role of CRT as a recommended treatment option for heart failure patients with dyssynchronous ventricular activation (Linde, Ellenbogen, & McAlister, 2012; Moynahan, Faris, & Lewis, 2005). Such abnormal ventricular activation may appear on an electrocardiogram (ECG) as a left bundle branch block (LBBB), right bundle branch block, or an interventricular conduction delay. The most common conduction abnormality is LBBB, where prolonged ventricular activation is associated with delayed activation of the posterior and/or lateral LV free wall (Auricchio et al., 2004; Strauss, Selvester, & Wagner, 2011).

The current iteration of a transvenous CRT implant has been shown to be a safe and cost-effective device therapy option that is well-tolerated, has a high success rate, and can significantly reduce patient mortality and hospitalization rates (Alonso et al., 2001; Bradley et al., 2003; Calvert et al., 2005; Feldman et al., 2005; M. Fox et al., 2007; Gamble et al., 2016; Gold et al., 2017; Leon, Abraham, Curtis, et al., 2005; Noyes et al., 2013; van Rees et al., 2011). Despite advancements with surgical techniques and pacing technology, approximately 30% of CRT recipients do not clinically benefit and/or exhibit echocardiographic evidence of LV reverse remodeling following implant (Auricchio & Prinzen, 2011). Causes of this non-response are multifactorial, and include: inadequacies in the preoperative assessment of intrinsic electrical dyssynchrony, ischemic cardiomyopathies and myocardial scarring, apical LV lead locations, and suboptimal device programming. Ancillary reports from clinical trials have provided insight on how patient selection prior to CRT implant affects response (e.g., LBBB conduction, wide QRS duration [QRSd], non-ischemic cardiomyopathy) (van Bommel et al., 2009). Other factors associated with

successful device implantation, such as patient coronary venous anatomy and lateral LV lead placement, have been well-established (Khan et al., 2009; Morgan & Delgado, 2009).

The potential clinical and echocardiographic benefit from CRT depends not only on patient selection and proper implantation to deliver effective resynchronization, but also on adequate postoperative management of pacing settings and configurations (Mullens et al., 2009). Furthermore, while patient selection and optimal LV lead placements have been extensively researched, less understood is how to optimize CRT devices, using either echocardiographic or electrocardiographic methodologies (Vernooy, van Deursen, Strik, & Prinzen, 2014). Despite that pacing parameters and configurations can be readily and noninvasively adjusted during a routine device interrogation, the identification of optimal pacing configuration requires the evaluation of a multitude of settings. Echocardiography is the most commonly used methodology in optimizing the atrioventricular and interventricular delays. However, echocardiography is resource-intensive and costly. It also suffers from high variability and poor sensitivity in detecting subtle differences in heart function (Chung et al., 2008; van Everdingen et al., 2016).

In comparison, the use of electrocardiography (ECG) in optimizing CRT devices is less complicated and expensive (Gage et al., 2018; Sweeney et al., 2014; Sweeney et al., 2010). Recent technology, known as the ECG belt, provides a more detailed assessment electrical dyssynchrony via the simultaneous acquisition of ventricular activation from multiple unipolar electrodes placed over the upper anterior and posterior torso (Bank et al., 2018). Previous research have observed that metrics derived from the investigational ECG belt correlate with hemodynamic changes at different LV lead locations during the CRT implant (Johnson et al., 2017), and can predict subsequent LV reverse remodeling (Gage et al., 2017).

This dissertation will focus on the use of multiple unipolar electrodes placed over the anterior and posterior upper torso in measuring electrical synchrony during CRT pacing. Specifically, the following topics will be addressed:

1. Adaptive cardiac resynchronization therapy algorithm and electrical synchrony
2. Relationship between QRSd and therapeutic window for CRT optimization

The second chapter of this dissertation reviews the current literature concerning heart failure and CRT. The literature review discusses the landmark randomized clinical trials that established the efficacy of

CRT in the treatment of heart failure with electrical dyssynchrony. The current CRT guidelines are also discussed, as well as the persistent issue of non-response to CRT. The multifactorial causes of non-response are addressed, with a particular interest in describing various postoperative optimization methodologies that includes echocardiography, device-based pacing algorithms, and electrocardiography. Chapter three evaluates and quantifies how an adaptive CRT pacing algorithm improves electrical synchrony. Chapter four discloses the effect of native QRSd and the corresponding potential for electrical resynchronization during atrial-synchronized LV-only pacing. The fifth chapter of the dissertation briefly summarizes the cumulative findings of the manuscripts, and mentions the clinical implications and potential areas for future research. The supplemental appendix provided at the end dissertation gives a detailed description of the investigational ECG belt system and the proprietary methodology used to quantify improvements in electrical synchrony.

CHAPTER 2. REVIEW OF THE LITERATURE

INTRODUCTION

Heart failure prevalence and healthcare costs

Heart failure (HF) with reduced systolic function is characterized by left ventricular (LV) contractile dysfunction, with decrements in cardiac output that are inadequate to meet metabolic requirements and result in venous congestion (Cowie et al., 1997; Kemp & Conte, 2012). Its etiology typically occurs from myocardial injury subsequent to various preexisting cardiovascular diseases, such as hypertension (Levy, Larson, Vasan, Kannel, & Ho, 1996), atherosclerosis and myocardial infarction (K. F. Fox et al., 2001), and/or valvular heart disease (Marciniak, Glover, & Sharma, 2017). Genetics, conventional risk factors (e.g., tobacco smoking, obesity) (Kenchaiah et al., 2002), and infiltrative cardiomyopathies (Pereira, Grogan, & Dec, 2018) are other determinants of HF.

Advances in pharmacologic therapy, predominantly with angiotensin-converting-enzyme inhibitors (F. Andersson, Cline, Ryden-Bergsten, & Erhardt, 1999), beta-blockers (Poole-Wilson et al., 2003), aldosterone antagonists (Pitt et al., 1999; Zannad et al., 2011), and angiotensin-receptor blockers (Cohn & Tognoni, 2001; McMurray et al., 2003), have improved prognosis. Notwithstanding, HF persists as the most frequent cause of hospitalization among older adults in the United States (Barold & Ritter, 2008; Chen, Normand, Wang, & Krumholz, 2011; Fang, Mensah, Croft, & Keenan, 2008; Jencks, Williams, & Coleman, 2009; Keenan et al., 2008; Ross et al., 2010). The healthcare cost of HF in the United States is high, and it is anticipated that it will continue to exert a significant burden on healthcare spending in the next decade due to a combination of the aging population, increased survival following myocardial infarction, and the widespread utilization of pharmaceutical drugs and development of life-prolonging device therapies (Benjamin et al., 2019; Heidenreich et al., 2013).

Left bundle branch block conduction

Decrements in systolic function can be causally related to electrical dyssynchrony, depicted on an electrocardiogram (ECG) as a prolonged QRS duration (QRSd) with either a left bundle branch block (LBBB), right bundle branch block (RBBB), or a non-specific interventricular conduction delay (IVCD)

QRS morphology (Abraham, 2006; Kass, 2005; Spragg & Kass, 2006). Left bundle branch block occurs in one third of HF patients (Chandraprakasam & Mentzer, 2015; Kashani & Barold, 2005; Linde et al., 2012), and is a significant predictor of worsening prognosis, sudden cardiac death, and all-cause mortality (Bader et al., 2004; Baldasseroni et al., 2002; Epstein et al., 2013; Iuliano et al., 2002). It may also be indicative of degenerative structural cardiac diseases that can deteriorate to possible LV mechanical dyssynchrony (Eriksson, Hansson, Eriksson, & Dellborg, 1998; Grines et al., 1989; Hamby, Weissman, Prakash, & Hoffman, 1983; Ozdemir et al., 2001; Prinzen et al., 1995).

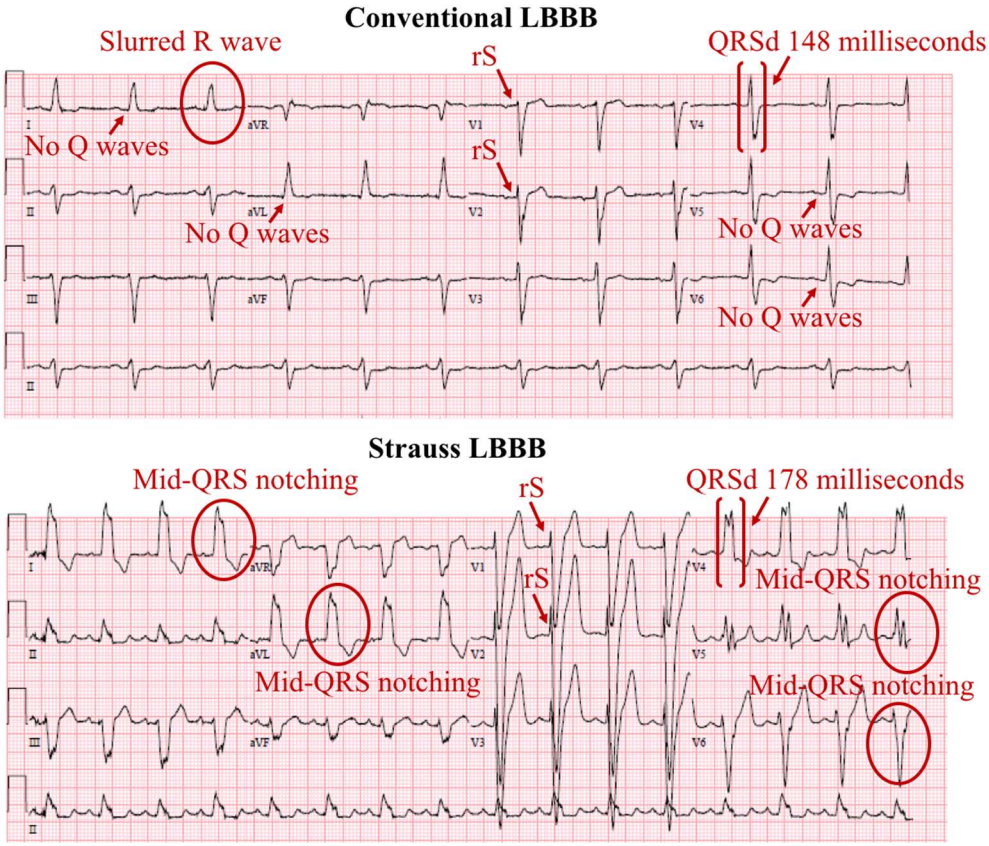

Figure 1. *Standard 12-lead ECGs of conventional LBBB and Strauss LBBB*

Conventional LBBB exhibits a slurred R wave with an absence of Q waves in the lateral leads (I, aVL, V_5, V_6). Strauss LBBB exhibits mid-QRS slurring or notching within at least contiguous two leads (I, aVL, V_5, V_6). Abbreviations: CRT, Cardiac resynchronization therapy; LBBB, Left bundle branch block; QRSd, QRS duration.

Intrinsic LBBB is associated with leftward septal depolarization, and then anterior-to-posterior LV depolarization (Strauss et al., 2011). Delayed activation of the lateral and posterolateral regions of the LV, with a U-shaped activation pattern that courses through the apex, are characteristic of LBBB conduction

(Auricchio et al., 2004; Jackson et al., 2014; Poole, Singh, & Birgersdotter-Green, 2016). Such dyssynchronous ventricular activation is manifested on a 12-lead ECG as a QRSd greater than 120 milliseconds, accompanied by dominant negative deflections in the anterior precordial leads (e.g., V_1, V_2), absence of Q waves in the lateral leads (e.g., aVL, I, V_5, V_6), and an initial slurring on the R-wave in the lateral leads (Anderson, 2018; Caputo et al., 2018) (Figure 1). Strauss proposed stricter criteria, including having a QRSd of at least 140 milliseconds for men and 130 milliseconds for women, in conjunction with mid-QRS notching or slurring in at least two contiguous leads (Strauss et al., 2011).

CARDIAC RESYNCHRONIZATION THERAPY

Innovations and the development of cardiac resynchronization therapy (CRT) were based on the premise that pacing both ventricles, either simultaneously or sequentially, in association to right atrial sensing and pacing could ameliorate the effects of electrical dyssynchrony and abnormal LBBB ventricular activation (Abraham, 2006; Auricchio, Stellbrink, et al., 1999; Nguyen et al., 2018). This device-based therapy utilizes a LV pacing lead in addition to the right atrial (RA) and right ventricular (RV) leads of a traditional dual-chamber pacemaker, or cardioverter-defibrillator, to create atrial-synchronized biventricular activation wavefronts (Figure 2) (Strik, van Middendorp, et al., 2013; Vernooy et al., 2014). The current iteration of CRT consists of a wholly transvenous implant, with pacing the LV epicardium from a lead placed in a coronary vein (Auricchio, Klein, et al., 1999).

Pacing leads are implanted into the RA and RV chambers, allowing for endocardial pacing and sensing of these chambers. The standard location for the RA lead is typically the right atrial appendage, but it can be implanted at different sites such as the lateral free wall (Belham, Gill, Gammage, & Holt, 2002; Jamidar, Goli, & Reynolds, 1993). The RV lead is usually implanted in either a septal or apical location. While some studies report worse outcomes with apical RV leads (Miranda et al., 2012; Riedlbauchova et al., 2006), the optimal RV lead location remains unresolved. Various clinical trials and a meta-analysis report no differences in response rates between apical and septal RV leads (Daimee et al., 2018; Khan et al., 2011; Kristiansen, Vollan, Hovstad, Keilegavlen, & Faerestrand, 2012; Leclercq et al., 2016; Thebault et al., 2012; Zografos et al., 2015).

A third lead is percutaneously placed into a lateral or posterolateral tributary coronary vein leading into the coronary sinus. Left ventricular leads have evolved from initially being unipolar, to bipolar, and finally quadripolar designs (van Everdingen, Cramer, Doevendans, & Meine, 2015). Quadripolar LV leads allow for the ability to electrically pace from 4 different anatomic locations, providing for multiple LV vector configurations (Oswald et al., 2015; Sperzel et al., 2012). As compared to bipolar LV leads, quadripolar leads reduce the risk of phrenic nerve stimulation (Behar et al., 2015; Boriani et al., 2016; Mehta, Shetty, Squirrel, Bostock, & Rinaldi, 2012), reduce mortality (Leyva et al., 2017; Turakhia et al., 2016), and have lower rates of implantation failure and post-operative lead dislodgement (Forleo et al., 2011; Forleo et al., 2015; Rijal et al., 2017).

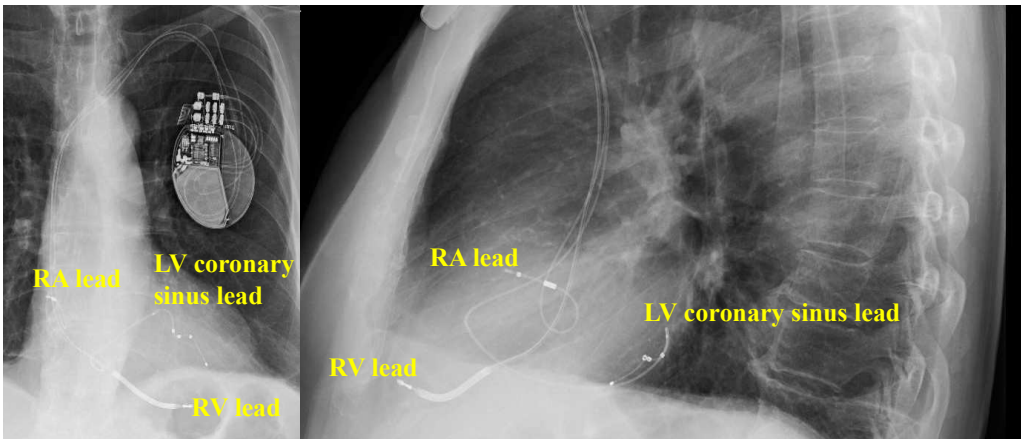

Figure 2. *Posteroanterior and lateral chest X-ray imaging of a CRT defibrillator*

The RV lead was implanted into an apical location, and the quadripolar LV lead was implanted into a lateral tributary coronary vein leading into the coronary sinus. Abbreviations: LV, Left ventricular; RA, Right atrial; RV, Right ventricular.

LANDMARK CLINICAL TRIALS AND EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES FOR CRT PATIENT SELECTION

The preliminary landmark trials that established CRT pacemakers and defibrillators as an effective device therapy option for improving outcomes in HF patients includes Pacing Therapies for Congestive Heart Failure (PATH-CHF) (Auricchio et al., 2003; Auricchio et al., 2002), Multisite Stimulation in Cardiomyopathies (MUSTIC) (Cazeau et al., 2001; Leclercq et al., 2002; Linde et al., 2002), and Multicenter InSync Randomized Clinical Evaluation (MIRACLE) (Abraham et al., 2002; Young et al.,

2003). These initial trials collectively showed that CRT decreases NYHA class and hospitalization rates, and improves exercise tolerance, peak oxygen consumption (i.e., VO_2), and quality of life (Table 1).

Improved LV reverse remodeling and systolic function following CRT were first reported in MUSTIC (Duncan, Wait, Gibson, & Daubert, 2003) and PATH-CHF (Stellbrink et al., 2001). Further evidence of LV reverse remodeling and improved systolic function were reported in CONTAK-CD (Higgins et al., 2003), as well as MIRACLE (St John Sutton et al., 2003), MIRACLE ICD (Abraham et al., 2004), Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) (Linde et al., 2008), and Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) (Moss et al., 2009). Survival benefit from CRT was demonstrated in Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) (Bristow et al., 2004), Cardiac Resynchronization-Heart Failure (CARE-HF) (Cleland et al., 2006; Cleland et al., 2005), and Resynchronization–Defibrillation for Ambulatory Heart Failure Trial (RAFT) (Tang et al., 2010).

Native QRSd in the selection of CRT candidates

Predictors of Response to CRT (PROSPECT) reported prolonged intrinsic QRSd predicted clinical and echocardiographic response (Chung et al., 2008; van Bommel et al., 2009). Several clinical trials and two meta-analyses have further observed consistent clinical and echocardiographic benefit in patients with a QRSd greater than 150 milliseconds (Auricchio et al., 2003; Bristow et al., 2004; Bryant, Wilton, Lai, & Exner, 2013; Moss et al., 2009; Sipahi, Carrigan, Rowland, Stambler, & Fang, 2011; Tang et al., 2010).

While prolonged QRSd and LBBB ventricular activation are indicative of electrical dyssynchrony, many patients with HF have a narrow QRSd (i.e., 120 to 130 milliseconds), and a significant proportion of these patients exhibit echocardiographic evidence of mechanical dyssynchrony (Achilli et al., 2003; Bleeker, Holman, et al., 2006; Bleeker et al., 2004; Ghio et al., 2004; Haghjoo et al., 2007; Tatsumi et al., 2011; Yu et al., 2006; Yu et al., 2003). The Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (ReThinQ) trial reported improved NYHA class in patients with a QRSd less than 130 milliseconds, but non-significant improvements in exercise capacity and LV reverse remodeling

(Beshai et al., 2007). Evaluation of Screening Techniques for Electrically-Normal, Mechanically Dyssynchronous HF Patients Receiving CRT (ESTEEM-CRT) observed minor improvements in LV dP/dt_{max}, but unchanged exercise capacity and LV reverse remodeling in patients with a QRSd less than 120 milliseconds (Donahue et al., 2012). Evaluation of Resynchronization Therapy for Heart Failure (Lesser-EARTH) (Thibault et al., 2013) and Echocardiography Guided Cardiac Resynchronization Therapy (ECHO-CRT) (Ruschitzka et al., 2013; Steffel et al., 2015) were two different clinical trials of narrow QRSd patients that were both prematurely stopped for futility concerns in response to the reported increased mortality, hospitalization rates, and worsened exercise tolerance.

While several trials of narrow QRSd patients report suboptimal and/or adverse outcomes from CRT (Shah, Patel, Molnar, Ellenbogen, & Koneru, 2015; Wang et al., 2015), Narrow QRS Ischemic Patients Treated with CRT (NARROW-CRT) observed improved survival from the combined endpoint of hospitalizations, mortality, and ventricular fibrillation (Muto et al., 2013). In sum, the usefulness of CRT in this specific population remains controversial, and the current guidelines do not recommend CRT in narrow QRSd patients (Ponikowski et al., 2016). The current understanding is that CRT may worsen or can provoke dyssynchrony in patients that exhibit little or no preoperative intrinsic electrical dyssynchrony. Additionally, the effectiveness of CRT in patients with a moderate QRSd that is between 120 to 150 milliseconds has generally not been supported in clinical trials (Moss et al., 2009).

Native QRS morphology in the selection of CRT candidates

The influence of LBBB QRS morphology with predicting favorable response has been extensively demonstrated (Bilchick, Kamath, DiMarco, & Stukenborg, 2010; Bristow et al., 2004; Hsu et al., 2012; Sipahi et al., 2012; Zareba et al., 2011). However, further research is needed to define the relative values of QRS morphology and QRSd for patient selection, predominately due to the issue of multicollinearity. For instance, LBBB patients generally have longer QRSd, and a greater portion of patients with ischemic cardiomyopathies have non-LBBB conduction (Gold et al., 2012). While van Bommel et al. (2009) reported QRSd predicted CRT response, other studies that use Strauss criteria report QRS morphology, and not QRSd, as a more important predictor (Tian et al., 2013). Two retrospective studies observed clinical

and echocardiographic response are largely determined by QRS morphology, and to a lesser degree by QRSd (Dupont et al., 2012; Peterson et al., 2013). An analysis of Medicare beneficiaries similarity reported LBBB predicted superior clinical benefit; the subset of patients with non-LBBB conduction that reportingly benefited from CRT had a prolonged QRSd greater than 180 milliseconds (Sundaram et al., 2017).

A substantial proportion of patients with non-LBBB conduction, including IVCD or RBBB, have received a CRT device (Auricchio, Lumens, & Prinzen, 2014; Ellenbogen, Wilkoff, Kay, Lau, & Auricchio, 2017). However, most trials have either failed to show benefit (Bilchick et al., 2010; Kawata et al., 2019; Nery, Ha, Keren, & Birnie, 2011; Poole et al., 2016), or do not recommend the use of CRT in RBBB patients (Egoavil, Ho, Greenspon, & Pavri, 2005). In addition, several trials report lower response rates in IVCD patients (Birnie, Ha, et al., 2013; Gold et al., 2012; Sipahi et al., 2012; Zareba et al., 2011). Overall, QRS morphology is an established determinant of response; in particular, LBBB conduction is associated with superior outcomes, while the efficacy of CRT in IVCD and RBBB is controversial.

European Society of Cardiology CRT guidelines

Multiple randomized clinical trials in over 10,000 patients have designated the role of CRT as a recommended treatment option for selected HF patients (Linde et al., 2012). In its early developmental phases, CRT was indicated for patients with severe systolic dysfunction and advanced HF. Nowadays, CRT has been shown to be beneficial in patients with less severe HF, and is indicated for a wider patient population (Al-Majed, McAlister, Bakal, & Ezekowitz, 2011). Findings from the aforementioned trials led to the current guidelines that recommend CRT as Class IA indicated for HF patients with LBBB conduction and a prolonged QRSd (i.e., greater than 150 milliseconds); CRT in LBBB patients with a moderate QRSd (i.e., between 130 to 149 milliseconds) is Class IB indicated (Ponikowski et al., 2016). The guidelines recommend CRT implantation as Class IIa indicated (Level of evidence B) for non-LBBB patients with a prolonged QRSd, and IIb indicated (Level of evidence B) for non-LBBB patients with a moderate QRSd (Ponikowski et al., 2016). Additionally, CRT implantation in patients with a narrow QRSd (i.e., <130 milliseconds) is contraindicated (Class IIIA) (Ponikowski et al., 2016).

Clinical trial	NYHA	QRSd	LVEF	Primary and Secondary Outcomes	Results
MUSTIC-SR (*n*=58) (Cazeau et al., 2001)	III	>150ms	<35%	***Primary***: 6MWT; ***Secondary***: QOL, VO_2, mortality, HF hospitalizations	CRT-P improved 6MWT, VO_2, QOL; HF hospitalizations decreased
MIRACLE (*n*=453) (Abraham et al., 2002)	III, IV	>130ms	<35%	***Primary***: NYHA, QOL, 6MWT; ***Secondary***: VO_2, LVEF, LVEDV, MR severity, HF hospitalizations	CRT-P improved 6MWT, VO_2, NHYA, LVEF, MR; hospitalizations decreased
PATH-CHF (*n*=41) (Auricchio et al., 2002)	III, IV	>120ms	<35%	***Primary***: VO_2, 6MWT; ***Secondary***: QOL, NHYA	CRT-P improved 6MWT and VO_2
MIRACLE ICD (*n*=369) (Young et al., 2003)	III, IV	>130ms	<35%	***Primary***: NYHA, QOL, 6MWT; ***Secondary***: VO_2, LVEF, LV volumes	CRT-D improved QOL, NHYA, and VO_2
CONTAK-CD (*n*=490) (Higgins et al., 2003)	II-IV	>120ms	<35%	***Primary***: Mortality, hospitalizations; ***Secondary***: 6MWT, VO_2, NYHA, LVEF, LV volumes	CRT-D improved 6MWT, VO_2, LVESV, LVESV, and LVEDV
PATH CHF II (*n*=86) (Auricchio et al., 2003)	II	>120ms	<35%	***Primary***: VO_2, 6MWT; ***Secondary***: QOL, NHYA	CRT-P/CRT-D improved 6MWT, VO_2, QOL, and NYHA
MIRACLE ICD II (*n*=186) (Abraham et al., 2004)	II	>130ms	<35%	***Primary***: NYHA, QOL, 6MWT; ***Secondary***: VO_2, LVEF, LV volumes	CRT-D improved NYHA, LVESV, LVEDV, and LVEF
COMPANION (*n*=1520) (Bristow et al., 2004)	III, IV	>120ms	<35%	***Primary***: Mortality, hospitalizations; ***Secondary***: Mortality	CRT-P/CRT-D reduced all-cause mortality and hospitalizations
CARE HF (*n*=813) (Cleland et al., 2005)	III, IV	>120ms	<35%	***Primary***: Mortality, HF hospitalizations; ***Secondary***: QOL, LVEF, LV volumes, MR	CRT-P reduced HF hospitalizations and mortality; improved LVEF, LVESI, MR
ReThinQ (*n*=172) (Beshai et al., 2007)	III	<130ms	<35%	***Primary***: VO_2; ***Secondary***: QOL, NHYA	CRT-D improved NYHA, but not VO_2 and hospitalizations
REVERSE (*n*=610) (Linde et al., 2008)	I, II	>120ms	<40%	***Primary***: HF clinical composite score; ***Secondary***: LVEF, LV volumes, HF hospitalizations	CRT-P/CRT-D reduced hospitalizations; improved LVESI, LVEDI, LVEF
MADIT-CRT (*n*=1820) (Moss et al., 2009)	I, II	>130ms	<30%	***Primary***: Mortality, non-fatal HF adverse events; ***Secondary***: LVEF, LV volumes	CRT-D reduced HF adverse events; improved LVESV, LVEDV, LVEF
RAFT (*n*=1798) (Tang et al., 2010)	II, III	>120ms	<30%	***Primary***: Mortality, HF hospitalizations	CRT-D reduced all-cause mortality and HF hospitalizations
LESSER-EARTH (*n*=85) (Thibault et al., 2013)	III,IV	<120ms	<35%	***Primary***: VO_2; ***Secondary***: NYHA, QOL, 6MWT, LVEV, LV volumes	CRT-D did not improve VO_2, clinical outcomes, or LV reverse remodeling.
ECHO-CRT (*n*=809) (Ruschitzka et al., 2013)	III,IV	<130ms	<35%	***Primary***: Mortality, HF hospitalizations; ***Secondary***: NYHA, QOL	CRT-D did not reduce mortality or HF hospitalizations
NARROW-CRT (*n*=233) (Muto et al., 2013)	II,III	<120ms	<35%	***Primary***: HF clinical composite score; ***Secondary***: HF hospitalization, HF death, spontaneous VF	CRT-D improved survival from VF, HF hospitalizations, and HF death

Table 1. *Results of the landmark CRT clinical trials*

Abbreviations: 6MWT, 6-Minute walk test; CRT-D, Cardiac resynchronization therapy defibrillator; CRT-P, Cardiac resynchronization therapy pacemaker; LVEDV, Left ventricular end-diastolic volume; LVEF, Left ventricular ejection fraction; LVESV, Left ventricular end-systolic volume; LVESVI, Left ventricular end-systolic volume index; MR, Mitral regurgitation; NYHA, New York heart association; QOL, Quality of life; QRSd, QRS duration; VF, Ventricular fibrillation; VO_2, Volume of oxygen consumed.

CURRENT STATE OF CRT AND THE ISSUE OF NON-RESPONSE

Despite explicit guidelines and advancements in pacing technology, CRT-treated patients are a heterogeneous group that display a wide variation in response. Approximately 30% of CRT recipients have consistently been considered non-responders, which includes the subset of patients that do not clinically improve and/or exhibit LV reverse remodeling (Auricchio & Prinzen, 2011; Daubert, Behar, Martins, Mabo, & Leclercq, 2017; Naqvi, Jawaid, Goldenberg, & Kutyifa, 2018). The prognosis of non-responders is exceptionally poor, associated with less than 50% survival at 5 years (Rickard et al., 2014). Non-responders are also passively managed; 44.1% reportingly receive no additional treatment following non-response diagnosis (N. Varma et al., 2019). Non-responders are more likely than responders to receive HF treatments, education training, and medication changes; however, these treatments have minimal impact on clinical outcomes, evidenced by higher hospitalization and mortality rates (N. Varma et al., 2019).

While the prevalence of non-response has moderately but progressively decreased over the past two decades, mostly in LBBB patients, non-response rates have largely remained unchanged in patients with non-LBBB conduction (Auricchio & Heggermont, 2018). Furthermore, the proportion of CRT recipients that are super-responders has not significantly changed, representing about 30% of all patients (Auricchio & Heggermont, 2018). The issue of non-response is thought to emanate from an amalgamation of inadequacies with assessing preoperative intrinsic electrical dyssynchrony, patient-specific differences in coronary venous anatomy and the LV lead location, myocardial fibrosis, and/or the paucity of routine patient-specific device optimization methodologies (Birnie & Tang, 2006).

Interobserver variability and lack of unanimity in diagnosing LBBB with CRT non-response

The ability of a prolonged intrinsic QRSd with predicting favorable outcomes has been extensively demonstrated. Nevertheless, QRSd provides only a general prediction of CRT response, and its predictive value is diminished by excessive interobserver variation (De Pooter, El Haddad, Stroobandt, De Buyzere, & Timmermans, 2017; De Pooter et al., 2016; Lund-Andersen, Petersen, Jons, Philbert, Tfelt-Hansen, et al., 2018; Mollema, Bleeker, van der Wall, Schalij, & Bax, 2007). One study reported up to 47% of QRSd values from a 12-lead ECG differed by more than 20 milliseconds when measured by multiple

cardiologists and/or ECG machines (De Guillebon et al., 2010). Furthermore, QRSd is a one-dimensional temporal index that provides limited insight into the underlying mechanical dysssynchrony, and may have low sensitivity in identifying delayed LV lateral wall activation (Auricchio & Yu, 2004; Engels, Mafi-Rad, van Stipdonk, Vernooy, & Prinzen, 2016; Kass, 2003; Mafi Rad et al., 2016).

The predictive ability of intrinsic electrical dyssynchrony is further complicated with reports that one-third of patients with conventional LBBB are misdiagnosed (L. G. Andersson et al., 2013; Auricchio et al., 2004; Risum et al., 2015). Misdiagnosis occur in the context of ventricular hypertrophy, during which the increase in ventricular wall thickness or chamber enlargement slows intramyocardial conduction velocity and, thereby, prolongs the QRSd above the diagnostic threshold of 120 milliseconds (Bacharova, Szathmary, Kovalcik, & Mateasik, 2010; Galeotti, van Dam, Loring, Chan, & Strauss, 2013; Quintanilla et al., 2017; Strauss et al., 2011; Surkova et al., 2017). Furthermore, LBBB diagnostic guidelines continue to evolve (Anderson, 2018; van Deursen et al., 2014), and dissimilarities between the European and American guidelines complicate a uniform diagnosis (Caputo et al., 2018; Kusumoto et al., 2019; Surawicz et al., 2009). Reports on the impact of stricter LBBB criteria has also been conflicting (Bertaglia et al., 2017; Emerek et al., 2015; Jastrzebski et al., 2018; Perrin et al., 2012; Tian et al., 2013). The combined interobserver variability and lack of unanimity in diagnosing LBBB may result in inconsistencies with assessing intrinsic electrical dyssynchrony, and likely contributes to non-response.

Ischemic HF etiology and connection with CRT non-response

Ischemic cardiomyopathies are another determinant of non-response (Diaz-Infante et al., 2005; Gasparini et al., 2003; Reuter et al., 2002; Ypenburg, Roes, et al., 2007; Ypenburg, Schalij, et al., 2007). Several trials and observational studies report clinical response and the magnitude of LV reverse remodeling is higher in non-ischemic cardiomyopathy patients (Barsheshet et al., 2011; Marsan, Bleeker, van Bommel, Ypenburg, et al., 2009; Martens et al., 2018; McLeod et al., 2011; Sutton et al., 2006; Wikstrom et al., 2009; Yokoshiki, Mitsuyama, Watanabe, Mitsuhashi, & Shimizu, 2017). Studies that use gadolinium delayed enhancement magnetic resonance imaging report an inverse relationship between the extent of myocardial scarring with subsequent clinical and echocardiographic response (Acosta et al., 2018;

Chalil et al., 2007; Harb et al., 2019; White et al., 2006). Extensive scar tissue localized to the tip of the LV lead, commonly the posterolateral wall, also particularly increases the risk of ineffective pacing (Adelstein & Saba, 2007; Bleeker, Schalij, Van Der Wall, & Bax, 2006; Bose et al., 2014; Daoulah et al., 2015).

Association of non-lateral LV leads with CRT non-response

Non-response is more likely to occur in patients with non-lateral LV leads implanted into an apical position within an anterior coronary vein (Kronborg et al., 2016). Apical LV leads have been associated with increased hospitalization and mortality rates (Singh et al., 2011), increased risk of ventricular tachyarrhythmias (Kutyifa et al., 2013), and unfavorable echocardiographic response (Thebault et al., 2012). Superiority of a lateral or posterolateral LV lead, as compared to an apical LV lead, has been extensively demonstrated (Butter et al., 2001; Kutyifa et al., 2018; Macias, Gavira, Castano, Alegria, & Garcia-Bolao, 2008; Rossillo et al., 2004; Rovner et al., 2007).

Suboptimal CRT programming as a prevailing source of CRT non-response

Suboptimal ventricular activation from insufficient postoperative management of pacing parameters is a prevailing cause of ineffective CRT pacing in a significant proportion of non-responders (Singh & Gras, 2012). Current CRT devices are capable of pacing both ventricles either simultaneously or separated by a specified biventricular offset interval (i.e., interventricular delay, sequential biventricular pacing), and after a specified atrioventricular delay with respect to the detection of an intrinsic atrial contraction, or an atrial paced beat (Cuoco & Gold, 2012). Atrial-synchronized LV-only pacing has recently become of interest as a form of CRT (Boriani et al., 2010; Gasparini et al., 2006; Lumens et al., 2013; Skaf et al., 2017; Thibault et al., 2011), with reports of it being superior to biventricular pacing in the select group of LBBB patients with intact atrioventricular conduction (Lee et al., 2007; Martin et al., 2012; van Gelder, Bracke, Meijer, & Pijls, 2005). In addition, CRT devices integrated with either bipolar or quadripolar leads enable optimizing the LV vector (O'Donnell et al., 2017).

The optimal atrioventricular and interventricular timings greatly differ between patients, and nominal CRT programming, typically at an empiric and predetermined atrioventricular delay with

simultaneous biventricular pacing, may result in pacing-induced dyssynchronous ventricular activation in some patients. Specifically, excessively short atrioventricular delays could exert delirious effects on LV function, due to the truncation of LV filling with the associated subsequent introduction of cannon atrial waves (Antonini et al., 2012; Cheng, Landman, & Stadler, 2012). Prolonged atrioventricular delays may also curtail CRT benefit by exacerbating mitral regurgitation (Bilchick, Helm, & Kass, 2007; Ellenbogen et al., 2017; Houthuizen, Bracke, & van Gelder, 2011). Inappropriate programming of the atrioventricular delay is a predominant causative factor of ineffective ventricular pacing, with reports of it being the largest contributor accounting for episodes of sustained loss of pacing (Cheng et al., 2012; Mullens et al., 2009).

While CRT devices are usually programmed at a default setting of simultaneous biventricular pacing, current devices allow for sequential pacing with different interventricular offset intervals between RV and LV activation (Cuoco & Gold, 2012; Gold et al., 2018; Mortensen et al., 2004; Sogaard et al., 2002). Typically LV preactivation is preferred since RV preactivation has seldomly been shown to be beneficial, and may actually result in decrements with LV function (Bogaard et al., 2012; Kurzidim et al., 2005). The subset of patients with LV latency particularly benefit and exhibit improved electrical synchrony from LV preactivation (Herweg et al., 2010; Herweg et al., 2006; Singh & Gras, 2012). The InSync III trial reported greater improvements in exercise capacity, with minor improvements in stroke volume, from echocardiographic optimized sequential biventricular pacing compared to a pharmacological control group (Leon, Abraham, Brozena, et al., 2005). Modest clinical benefit from echocardiographic optimized sequential biventricular pacing, as compared to simultaneous pacing, was demonstrated in a different randomized trial (Abraham et al., 2012). On the contrary, other trials have observed no additional benefit from interventricular delay optimization (Boriani et al., 2006; Rao et al., 2007). Discrepancies between studies may be attributable to differences in optimization methodologies. Patients with ischemic cardiomyopathy and LV latency derive greater benefit from LV preactivation (Marsan, Bleeker, Van Bommel, Borleffs, et al., 2009; van Gelder, Bracke, Meijer, Lakerveld, & Pijls, 2004); thus, differences in patient demographics and HF etiology may also explain the aforementioned conflicting results.

UNDERUTILIZATION OF CRT DEVICE OPTIMIZATION

Optimization of the atrioventricular and interventricular intervals are not performed as standard of clinical care in a significant proportion of patients. It has been reported that nearly 58% of investigators do not optimize CRT devices (Gras et al., 2009). In routine clinical practice, less than 30% of responders, and 50% of non-responders, even have their device settings changed following implant (N. Varma et al., 2019). While CRT settings can be readily and noninvasively modified through the device programmer, the identification of the optimal setting requires evaluation of a myriad of pacing configurations (van Deursen et al., 2014). The complexity of selecting different pacing configurations and the advent of new features, such as adaptive pacing algorithms and multipoint pacing (Niazi et al., 2017; Pappone et al., 2015), may partly explain why device CRT optimization is underutilized.

Consequently, patients are often set at their nominal device settings following implant, with no electrocardiographic or echocardiographic assessment of how CRT affects ventricular activation. While multiple echocardiographic and non-echocardiographic methods have been proposed to optimize CRT devices, there is no methodology that has been generally accepted in standard of care clinical medicine. The lack of a standardized, patient-specific method in programming CRT devices has remained to be a persistent unresolved issue. Furthermore, the high variability in HF etiology and heart anatomy between patients emphasizes the need for the widespread utilization of a patient-specific approach with programing the atrioventricular and interventricular timings, as well as selecting the LV pacing vector.

CRT DEVICE OPTIMIZATION METHODOLOGIES

Echocardiographic optimization

Several echocardiographic methodologies to optimize the atrioventricular delay have been used in both research and clinical practice, and include the following: Ritter (Kindermann, Frohlig, Doerr, & Schieffer, 1997; Ritter, Daubert, Mabo, Descaves, & Gouffault, 1989), Iterative (Jones et al., 2014; Raphael et al., 2013), mitral inflow velocity time integral (Jansen et al., 2006), aortic velocity time integral (Kerlan et al., 2006), and LV dP/dt_{max} (Whinnett et al., 2013). Interventricular optimization is typically programmed via aortic velocity time integral methodology (Barold, Ilercil, & Herweg, 2008; Cuoco & Gold, 2012).

While echocardiography has traditionally been the most frequently used optimization technique, it is time and resource-intensive (Gras et al., 2009). In addition, it is not sensitive enough to detect subtle improvements in LV mechanical synchrony with changes in device settings. In light of its logistically challenging nature to perform accurately, echocardiographic optimization is generally only performed on non-responders and in highly specialized and experienced laboratories. Multi-center data suggests echocardiographic optimization methodologies lack precision (Chung et al., 2008), and recent trials report it to be noninferior to standard simultaneous biventricular pacing (Ellenbogen et al., 2010).

CRT device-based ambulatory pacing algorithms

Device-based pacing algorithms that are proprietary to various medical device companies have been developed, enabling individualized ambulatory optimization of CRT settings and configurations (Abraham et al., 2010; Brugada et al., 2014; Cuoco & Gold, 2012; Daoud & Houmsse, 2016; Ellenbogen et al., 2010; Filippatos et al., 2017; Krum et al., 2012). Post-hoc analysis observed superior clinical and echocardiographic benefit from ambulatory device optimization within the select group of CRT recipients in sinus rhythm (Birnie, Lemke, et al., 2013; Burns, Gage, Curtin, Gorcsan, & Bank, 2017; Hsu et al., 2019). However, the effectiveness of pacing algorithms in reducing non-response rates still largely remains unresolved, and superiority versus echocardiography has yet to be unanimously established (Brugada et al., 2017; Ellenbogen et al., 2010; Kamdar et al., 2010; Martin et al., 2012). The current understanding is that pacing algorithms are cost-effective and less resource-intensive relative to echocardiography, and shows promise with improving clinical outcomes and reducing hospitalization rates (Birnie et al., 2017; Gasparini et al., 2019; Ritter et al., 2012; Singh et al., 2013; Starling et al., 2015).

Electrocardiographic optimization

Various electrocardiographic optimization methods have been proposed, with the vast majority being based on surface 12-lead ECGs (Lund-Andersen, Petersen, Jons, Philbert, Vinther, et al., 2018; Pujol-Lopez et al., 2019; Vernooy, Verbeek, et al., 2007) and/or vectorcardiogram metrics that includes QRS area

and QRS vector (Burch, 1985; Kors, van Herpen, Sittig, & van Bemmel, 1990; van Deursen, Vernooy, et al., 2015).

Long-term stability of QRSd narrowing during uncomplicated biventricular CRT pacing was initially documented in MUSTIC (Linde et al., 2002). Two different multi-center trials reported associations between QRSd narrowing with subsequent clinical benefit (Gold et al., 2012; Hsing et al., 2011). Improvements in acute hemodynamics (Arbelo et al., 2014; Derval et al., 2014), long-term echocardiographic response (Kamireddy, Agarwal, Adelstein, Jain, & Saba, 2009) and reductions in mitral regurgitation severity (Karaca et al., 2016) with QRSd narrowing have been since been observed in smaller studies. Further evidence on the association between QRSd narrowing with favorable clinical outcomes has documented in several non-randomized observational studies (Alonso et al., 1999; Bonakdar et al., 2009; Coppola et al., 2016; Lecoq et al., 2005; Molhoek et al., 2004; Rickard et al., 2013; Rickard et al., 2012; Rickard et al., 2011; Yang et al., 2014). A meta-analysis additionally reported QRSd narrowing predicted both clinical and echocardiographic outcomes (Korantzopoulos, Zhang, Li, Fragakis, & Liu, 2016), and a retrospective study observed QRSd narrowing predicted long-term survival (Jastrzebski et al., 2019). Superiority of device optimization guided by QRSd narrowing with improving LV reverse remodeling compared to echocardiographic optimization (Tamborero et al., 2011), and also standard simultaneous biventricular pacing (Trucco et al., 2018), was demonstrated in two different prospective randomized trials.

Vectorcardiography has become a recent focus in CRT device optimization research. Preliminary studies in canine models (van Deursen et al., 2012), and later in humans (De Pooter, El Haddad, De Buyzere, et al., 2017; van Deursen, Wecke, et al., 2015), reported improvements in acute hemodynamics correlated with reductions in QRS area during CRT pacing. The ability of intrinsic QRS area in predicting echocardiographic response (van Deursen, Vernooy, et al., 2015), and also survival from a composite endpoint of either heart transplantation and ventricular assist device implant (Emerek et al., 2019), has been documented in two different retrospective studies. Still, superiority of vectorcardiographic device optimization as compared to other methodologies, including echocardiography, has yet to be conducted in a prospective randomized trial.

ELECTRICAL WAVEFRONT FUSION AND CANCELLATION DURING CRT PACING

Electrocardiographic analysis of paced ventricular activation and amelioration of electrical dyssynchrony

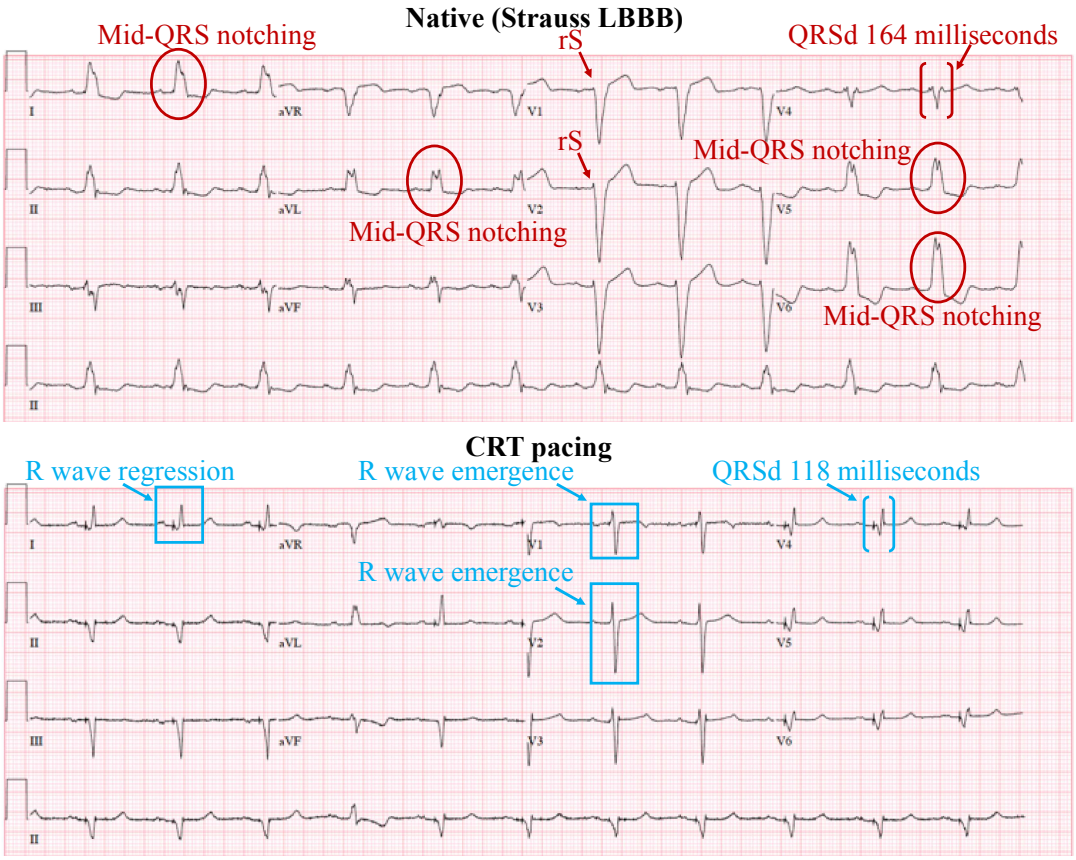

Figure 3. *Comparisons of 12-lead ECGs displaying native Strauss LBBB conduction, and evidence of wavefront fusion and cancellation during CRT pacing*

Electrocardiographic evidence of wavefront fusion and cancellation during CRT pacing was observed by R wave emergence in the anterior precordial leads (e.g., V_1, V_2), R wave regression in the lateral leads (e.g., I), QRSd narrowing in all leads, and a frontal axis deviation shift. Abbreviations: CRT, Cardiac resynchronization therapy; LBBB, Left bundle branch block; QRSd, QRS duration.

Paced CRT activation reflects ventricular fusion and electrical cancellation of three distinct wavefronts, including the native, RV paced, and LV paced wavefronts (Barold & Herweg, 2011b; Cooper, Patel, Emmi, Wang, & Kirkpatrick, 2014). Ameliorations in electrical dyssynchrony emerge from fusion between an anterior and rightward electrical wavefront from the LV lead, with a posterior wavefront that moves leftward, either from the RV lead and/or the native wavefront (Strik, van Middendorp, et al., 2013; Sweeney et al., 2010). This fusion can be identified by not only reduced QRSd, but also via morphological changes in ventricular activation that represent destructive interference from opposing wavefronts (Barold,

Giudici, Herweg, & Curtis, 2006; Barold, Herweg, & Giudici, 2005; Barold & Ritter, 2008; van Stipdonk, Wijers, Meine, & Vernooy, 2015). In particular, R wave emergence within the anterior precordial leads (e.g., V_1, V_2), R wave regression in the lateral leads (e.g., I, aVL), and right-axis frontal deviation shift are characteristic of improved wavefront fusion and cancellation (Figure 3) (Sweeney et al., 2010). Such improvements in electrical synchrony and ventricular fusion can particularly be achieved by optimizing the atrioventricular and interventricular timings, and also by adjusting pacing configurations between biventricular and atrial-synchronized LV-only pacing (van Deursen et al., 2014).

Effect of atrioventricular delay optimization during simultaneous biventricular pacing

During simultaneous biventricular pacing, and in CRT devices integrated with LV pacing from a lateral or posterolateral coronary vein, QRS fusion complexes for LBBB patients in sinus rhythm should ideally be characterized by the appearance of an R wave in V_1 (Figure 4) (Barold et al., 2005). However, imbalanced fusion might be observed at short atrioventricular delays, as identified by a dyssynchronous RBBB pattern of depolarization in V_1 that is attributable to the prevailing paced ventricular wavefronts that precede the native wavefront (Figure 4) (Barold et al., 2005). Prolonged atrioventricular delays may also frequently be associated with imbalanced ventricular fusion, as evidenced by a negative QRS fusion complexes in V_1 (Figure 4). Such imbalanced fusion is characterized by a prominent and dyssynchronous posteriorly-moving wave of depolarization, composed of the prevailing native wavefront that activates the ventricles prior to the paced wavefronts (Cooper et al., 2014).

Persistent negative QRS fusion complexes in V_1 during simultaneous biventricular pacing that occur regardless of atrioventricular optimization represent imbalanced ventricular activation, characterized by a preeminent posteriorly-moving native and/or RV paced wavefront with minimal fusion from the LV paced wavefront (Figure 5). Simultaneous biventricular pacing may particularly disproportionately favor the RV paced wavefront contribution in the context of heterogeneous impulse propagation and myocardial excitability, as observed with LV latency (Barold & Herweg, 2011b; Cooper et al., 2014; Pujol-Lopez et al., 2019). A negative complex in V_1 with uncomplicated pacing could also be attributable to suboptimal LV lead positions, potentially in either an anterior or middle coronary vein (Barold et al., 2006). The loss of

LV capture, sometimes related to LV lead dislodgement, may be another explanation for negative fusion complexes in V_1 (Barold et al., 2005).

Importance of interventricular delay optimization with LV preactivation in the context of LV latency

In the presence of LV latency, optimizing the atrioventricular delay during simultaneous biventricular pacing typically corresponds with negligible improvements in ventricular fusion. Such delayed activation and excitability may require correction via LV preactivation by adjusting the interventricular timing (Cooper et al., 2014). Patients with LV latency usually display LBBB ventricular activation in V_1 during simultaneous pacing, and a morphology intermediate between a LBBB and RBBB following interventricular optimization (Figure 6) (Barold et al., 2006; Barold & Herweg, 2011a; Berruezo et al., 2004; Herweg et al., 2010; van Deursen et al., 2014).

Atrioventricular delay optimization during atrial-synchronized LV-only pacing

Right ventricular pacing resembles LBBB activation in the precordial leads, characterized by a dominate paced wavefront originating from the RV lead that traverses posteriorly (Barold et al., 2006; Barold et al., 2005; Cooper et al., 2014) (Figure 7). Atrial-synchronized LV-only pacing, representing fusion between the LV paced wavefront and the native wavefront from the intact atrioventricular node and/or right bundle branch, exhibits substantial changes in electrical synchrony with atrioventricular delay optimization. Ventricular activation at short atrioventricular delays reflects imbalanced fusion that is disproportionately influenced by the anteriorly-moving paced wavefront from the LV lead that precedes the native wavefront. Optimal electrical synchrony and ventricular fusion typically occurs at an intermediate atrioventricular delay, after which subsequent prolongation of the atrioventricular delay causes the fusion complexes to reverse in polarity in V_1. At prolonged atrioventricular delays, ventricular fusion largely resembles native LBBB conduction, attributable to a greater contribution of the posteriorly-moving native wavefront, and with minimal fusion from the LV paced wavefront.

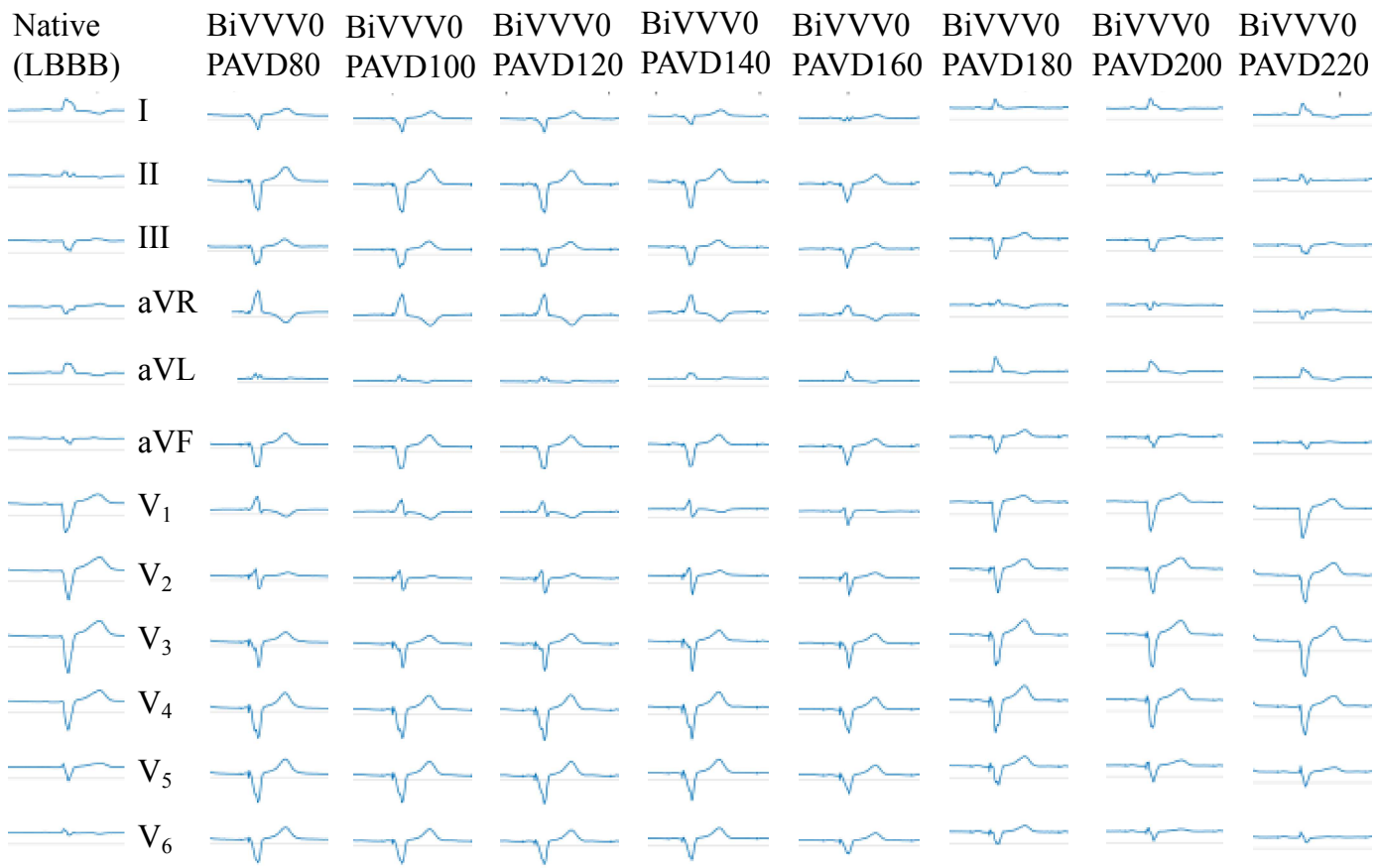

Figure 4. *Atrioventricular delay optimization during simultaneous biventricular pacing in a LBBB patient in sinus rhythm*

Data was acquired at paced atrioventricular delays that ranged from 80 to 220 milliseconds. Ventricular activation at short atrioventricular delays (e.g., 80 milliseconds) was characterized by a prominent R wave in V_1, representing fusion between the RV and LV paced wavefronts, but with minimal native contribution. Ventricular activation at prolonged atrioventricular delays (e.g., 220 milliseconds) predominately resembled native conduction, with a dominant negative QRS complex in V_1 that is composed of minimal fusion from the paced ventricular wavefronts. Abbreviations: BiVVV0, Simultaneous biventricular pacing; LBBB, Left bundle branch block; PAVD, Paced atrioventricular delay

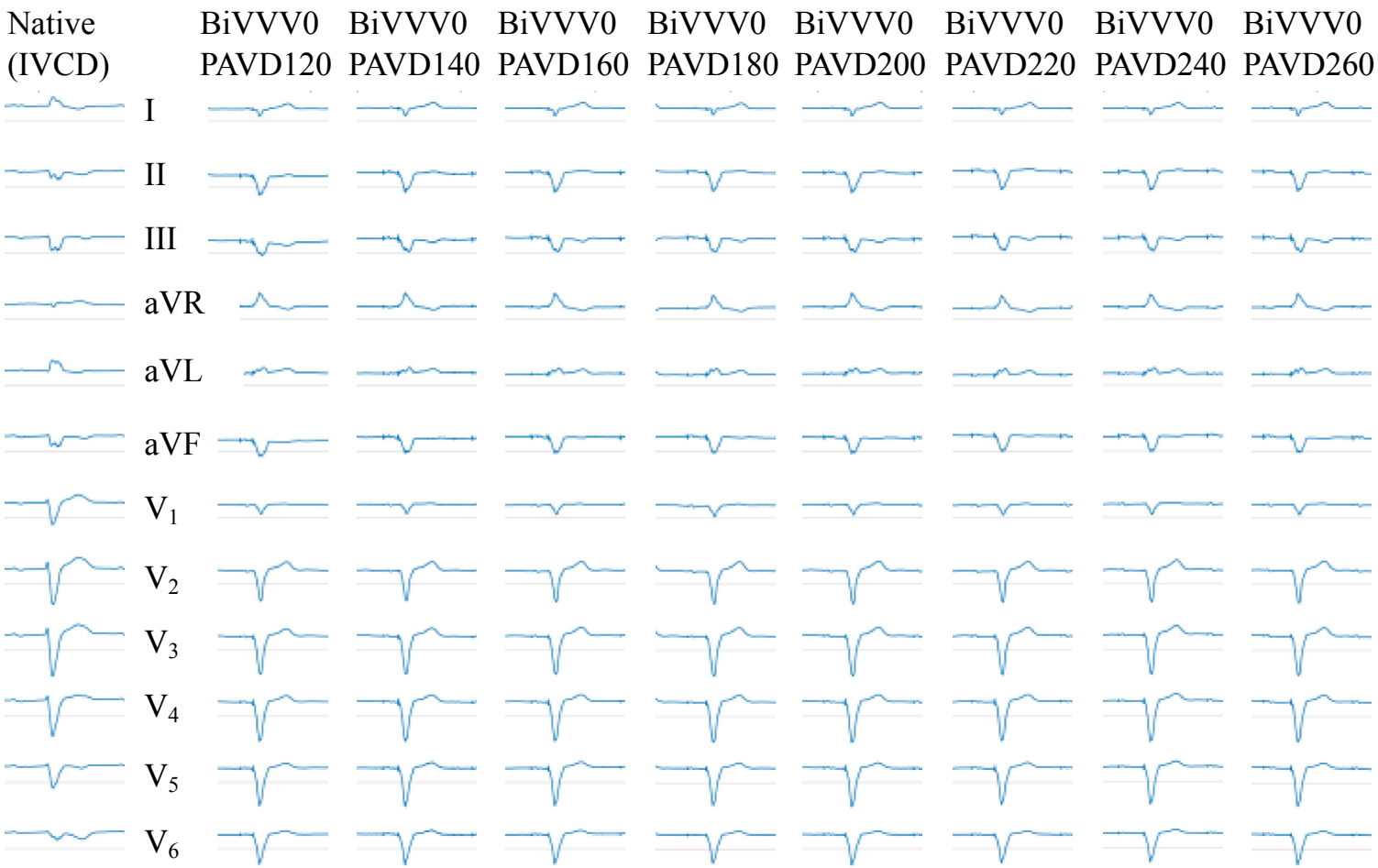

Figure 5. *Effect of LV latency on persistent dyssynchronous electrical ventricular activation irrespective of atrioventricular delay optimization during simultaneous biventricular pacing*

Data was acquired at paced atrioventricular delays that ranged from 120 to 260 milliseconds. Imbalanced ventricular fusion was evidenced by negative deflections in V_1 that persisted irrespective of optimizing the atrioventricular delay. This indicates posteriorly-moving wavefronts consistently exerted a greater contribution to ventricular activation than the LV paced wavefront. Abbreviations: BiVVV0, Simultaneous biventricular pacing; IVCD, Interventricular conduction delay; PAVD, Paced atrioventricular delay.

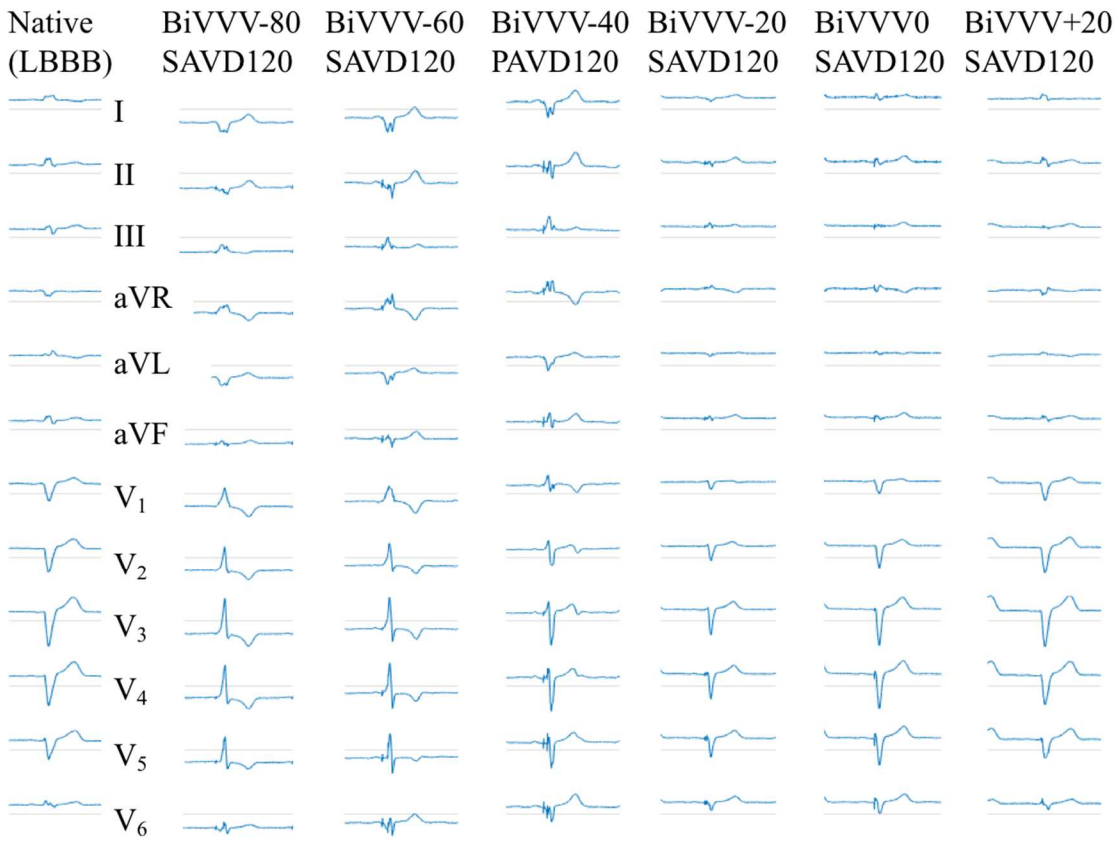

Figure 6. *Importance of interventricular delay optimization in improving electrical synchrony in the context of LV latency*

Negative interventricular delays indicate LV preactivation; BiVVV-20, BiVVV-40, BiVVV-60, and BIVVV-80 represent 20, 40, 60, and 80 milliseconds of LV preactivation, respectively. Positive interventricular delays represent RV preactivation. LV latency was present during simultaneous biventricular pacing at a sensed atrioventricular delay of 120 milliseconds, as depicted by a negative ventricular fusion complex in V_1. *Sequential biventricular pacing with LV pre-activation resulted in improved fusion from the anteriorly-moving LV paced wavefront, as depicted by the emergence of an R wave in* V_1 *at an interventricular delay with 40 milliseconds of LV preactivation. Abbreviations: BiVVV0, Simultaneous biventricular pacing; LBBB, Left bundle branch block; SAVD, Sensed atrioventricular delay.*

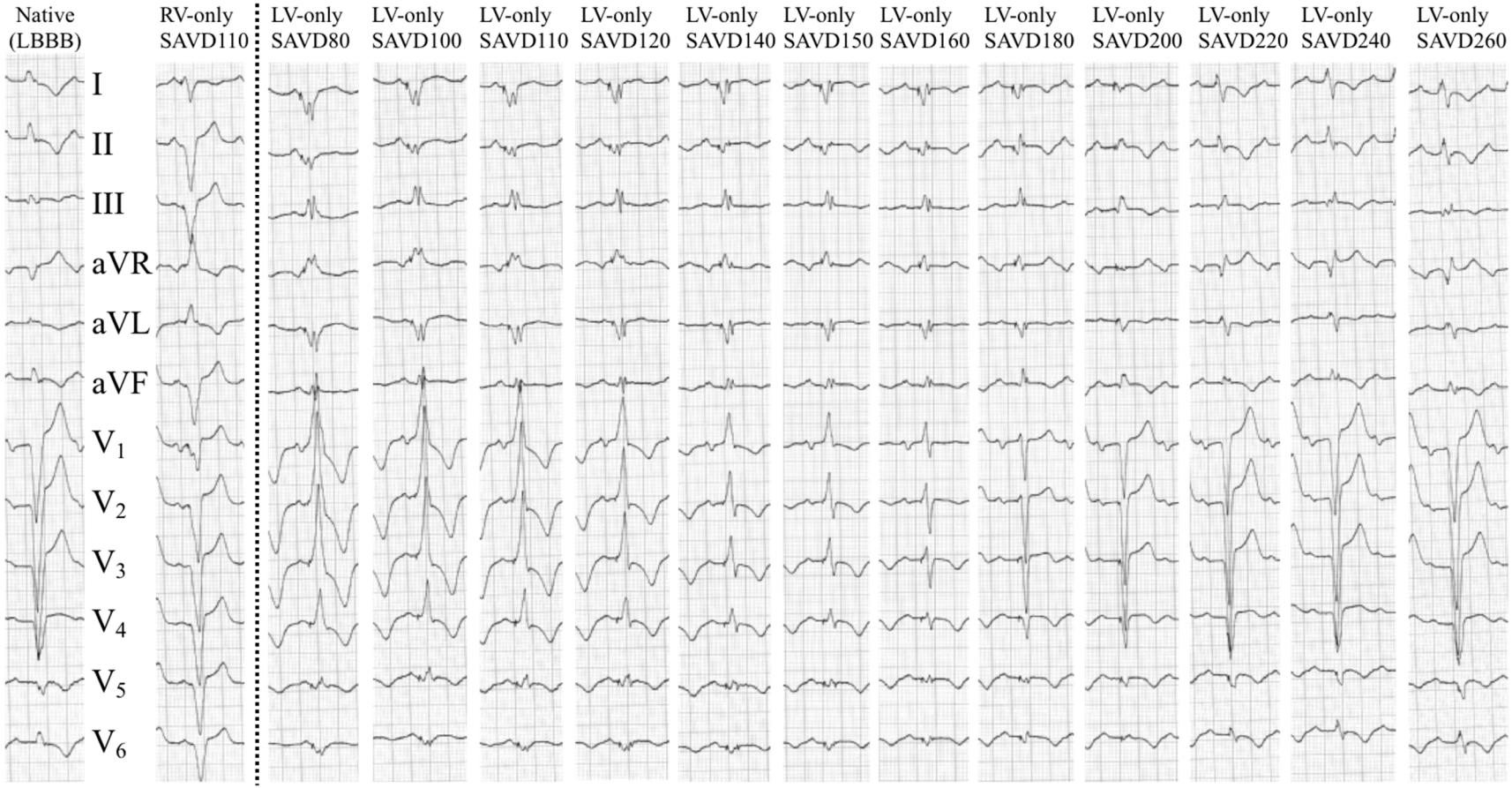

Figure 7. *Atrioventricular delay optimization during atrial-synchronized LV-only pacing in a LBBB patient in sinus rhythm*

Short atrioventricular delays (e.g., 80 milliseconds) are characterized by a prominent R wave in V_1, indicative of a dominant anteriorly-moving LV paced wavefront that precedes and depolarizes the myocardium prior to the native wavefront. Prolonged atrioventricular (e.g., 260 milliseconds) delays resemble native conduction, with dominant negative deflections in V_1 representing imbalanced ventricular fusion characterized by the prevailing posteriorly-moving native wavefront that precedes the LV paced wavefront. Optimal electrical synchrony occurred at an atrioventricular delay of 160 milliseconds, as manifested by frontal axis deviation shift, emergence of an R wave in V_1, and a general narrowing of the QRSd in all leads. Abbreviations: LBBB, Left bundle branch block; SAVD, Sensed atrioventricular delay.

Association of wavefront fusion and cancellation with subsequent echocardiographic response

Sweeney and colleagues demonstrated the following electrocardiographic evidence of wavefront fusion and cancellation during the paced rhythm as significant predictors of echocardiographic response: 1) rightward frontal axis deviation shift, 2) emergence of rightward forces within leads that have dominant leftward forces, 3) emergence of anterior forces in leads with dominant posterior forces, and 4) change in R wave amplitude in the expected direction within the lateral and precordial leads (Sweeney et al., 2010). The emergence of rightward forces was evidenced by R wave regression in the lateral leads (e.g., I and aVL); the emergence of anterior forces consisted of R wave emergence in the anterior precordial leads (e.g., V_1 and V_2). Increased R wave amplitudes in V_1 and V_2 that were at least 4.5 times that of intrinsic rhythm were particularly associated with increased probability of LV reverse remodeling (Sweeney et al., 2010).

In a follow-up study, Sweeney et al. (2014) reported two categories of ventricular fusion, as observed in leads V_1 and V_2 that predict echocardiographic response. This included either a QRS normalization fusion complex depicted by reduced QRSd without the emergence of a R wave, or a QRS conformational hybrid fusion complex characterized with a new or increased R wave. The highest response was observed with QRS normalization, of which occur when the paced ventricular wavefronts are highly oppositional and wavefront cancellation reduces the QRSd (Sweeney et al., 2014). Unless if there was a large reduction in QRSd, QRS conformational hybrid fusion complexes were less efficient in predicting response (Sweeney et al., 2014). A third type of QRS contour consisted of a persistent LBBB morphology with no new R wave, and either a neutral or increased QRSd. Persistent LBBB QRS fusion complexes, which were associated with the lowest response, emanate from non-oppositional paced wavefronts that constructively reinforce to generate dyssynchronous ventricular activation (Sweeney et al., 2014).

DEVICE OPTIMIZATION ON ELECTROCARDIOGRAPHIC CHARACTERISTICS OF WAVEFRONT FUSION AND CANCELLATION

Electrocardiographic evidence of LBBB activation reversal has previously been reported to predict acute hemodynamic response (Bogaard et al., 2012). In a case-control study, Gage et al. (2018) researched the effectiveness of electrocardiographic optimization, as based on the aforementioned principles of

wavefront fusion and cancellation, with improving systolic function in 130 patients with a de novo CRT device. In patients with nonischemic cardiomyopathies, as diagnosed by the absence of delayed enhancement on cardiac magnetic resonance imaging, electrocardiographic device optimization resulted with similar improvements in LV systolic function as compared to the subset of control patients that were not optimized and had standard CRT programming (Gage et al., 2018). Conversely, patients with either midwall stripe or ischemic pattern scar delayed enhancement exhibited superior improvements in LV systolic function following device optimization (Gage et al., 2018).

Although reductions in QRSd and qualitatively assessing wavefront fusion and cancellation on 12-lead ECGs have been associated with favorable response, superiority to echocardiographic optimization has yet to be established. QRS duration shortening may also be an oversimplification of the underlying fusion between the paced wavefronts and, thus, may not necessarily be reflective of good ventricular activation (Pujol-Lopez et al., 2019). Furthermore, assessing improvements in ventricular fusion complexes across different pacing configurations are usually not evident during a routine clinical device interrogation. Optimizing CRT devices as based on electrocardiographic characteristics of wavefront fusion and cancellation is onerous and, therefore, seldomly performed (van Deursen et al., 2014).

NON-INVASIVE ALTERNATIVES TO 12-LEAD ELECTROCARDIOGRAMS

High-resolution three-dimensional electrocardiographic mapping systems

Emerging technology that is composed of arrays of multiple unipolar electrodes placed over the upper torso is thought to provide a more detailed assessment of ventricular electrical activation as compared to a standard 12-lead ECG (Cuculich et al., 2011; Jia et al., 2006; Marrus, Andrews, Cooper, Faddis, & Rudy, 2012; Ramanathan, Ghanem, Jia, Ryu, & Rudy, 2004; Ramanathan, Jia, Ghanem, Ryu, & Rudy, 2006; Strik, Ploux, Jankelson, & Bordachar, 2019). Preliminary research investigated a noninvasive electrocardiographic imaging system that utilized 252 electrodes integrated with computed tomography (Ploux et al., 2015). Metrics derived from this technology were superior in predicting echocardiographic response than both QRSd and QRS morphology (Ploux et al., 2013). However, limitations included

complexity, cost, extensive time needed to analyze data, and the use of computed tomography that required intravenous contrast.

ECG belt investigational body surface mapping system

A single-use disposable ECG belt that does not require computed tomography imaging has been recently investigated (Figure 8) (Bank et al., 2018; Gage et al., 2017; Gage et al., 2018; Johnson et al., 2017; Rickard et al., 2020). The current ECG belt consists of a total of 17 and 36 unipolar electrodes adhered to the anterior and posterior upper torso, respectively (Verathon Inc, Bothell, WA, and modified by Medtronic plc, Mounds View, MN). Preliminary research of this ECG belt quantified ventricular electrical heterogeneity via isochronal activation mapping and activation time metrics, as derived from a proprietary software algorithm that automatically detects QRS complexes from the multichannel electrograms (Curtin, Burns, Bank, & Netoff, 2018).

In particular, the standard deviation of the activation times assessed ventricular electrical heterogeneity. For each ECG, the local body surface activation event, based on an extension on contact mapping principles, was the point of the steepest negative slope during the QRS complex in each of the 53 unipolar electrocardiograms (Bank et al., 2018; Gage et al., 2017; Johnson et al., 2017). The local body surface activation times were calculated with reference to the earliest recorded local activation event, and interpolated to construct isochronal activation maps. Standard deviation of the activation times have been shown to correlate with hemodynamic changes with different LV lead locations at CRT implant (Johnson et al., 2017), and can also predict echocardiographic response (Gage et al., 2017).

Average paired difference in the areas under the multiple pairs of anterior and posterior curves as a novel metric of electrical dyssynchrony

The average paired difference between the area under the curves (AUC) from the anterior and every posterior electrocardiograms is another metric derived from the ECG belt (Bank, Gage, Schaefer, Burns, & Brown, 2020). Cardiac resynchronization index (CRI) is a measure of percent electrical resynchronization, and calculated as the relative improvement in AUC at any given CRT pacing setting

normalized to native conduction. Currently under investigation, and included in the analysis for this dissertation, is the ability of CRI to quantify relative improvements in electrical synchrony during CRT pacing. Detailed descriptions of these metrics are provided in the appendix.

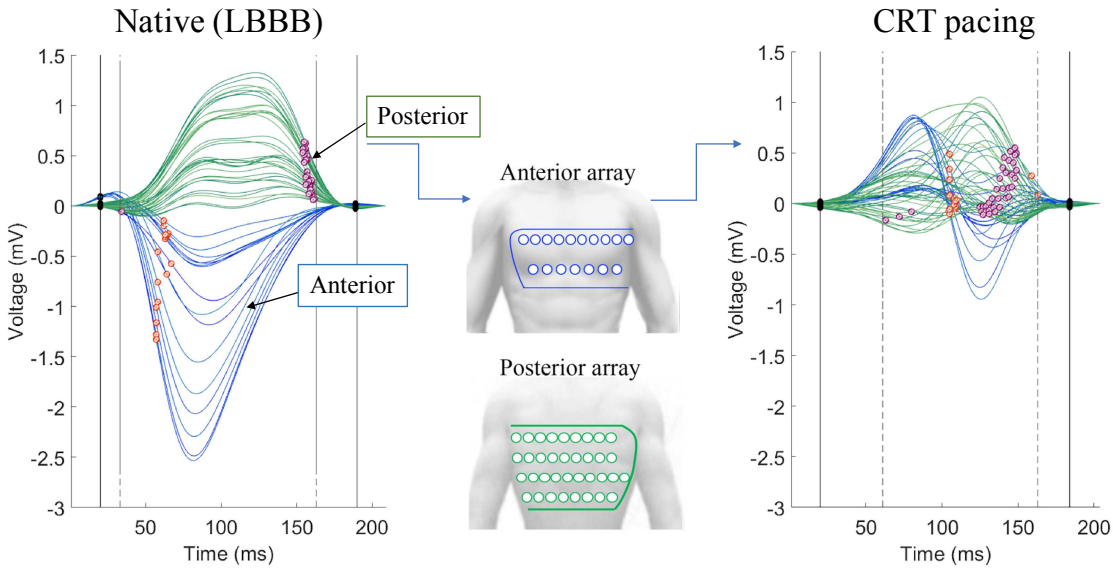

Figure 8. *Diagram of electrode placement for the investigational ECG belt system, and body surface multichannel electrocardiograms during native conduction and CRT pacing*

Signals recorded from the anterior electrocardiograms are displayed as blue, while signals recorded from the posterior electrocardiograms are green. Patient's native rhythm is representative of typical LBBB conduction, displaying a unidirectional wavefront that moves posteriorly, with negative deflections in the anterior electrodes and positive deflections in the posterior electrodes. The programmed CRT settings were atrial-synchronized LV-only pacing at a sensed atrioventricular delay of 130 milliseconds. CRT pacing resulted in reduced amplitude of the anterior and posterior electrocardiograms, associated with reversed polarity and an initial positive deflection in the anterior leads. Abbreviations: CRT, Cardiac resynchronization therapy; LBBB, Left bundle branch block.

SUMMARY AND CLINICAL IMPLICATIONS OF THE ECG BELT IN DEVICE OPTIMIZATION

CRT pacemakers and defibrillators have become an established device therapy option for patients with HF and electrical dyssynchrony; over a million patients have received a CRT device in the United States within the past decade. Despite improvements in pacing technology and surgery, 30% of CRT recipients are non-responders and consistently do not exhibit clinical and/or echocardiographic improvements. This persistent issue of non-response calls for improvements in patient-specific CRT device optimization methodologies. While the feasibility and effectiveness of echocardiography in programming

CRT devices is unresolved, 12-lead ECGs are less resource intensive and can accurately measure electrical wavefront fusion and cancellation.

Newer, novel technologies involve placing multiple unipolar electrodes across the anterior and posterior surface of the upper torso, allowing for a more global assessment of electrical wavefront fusion and cancellation as compared to standard 12-lead ECG methodologies. This technology shows promise in improving patient selection prior to implant, and also predicting clinical and echocardiographic response. This dissertation will focus on the use of CRI, a novel electrocardiographic measure of wavefront fusion and cancellation, in optimizing device programming. Two specific studies will be performed to demonstrate how CRI can quantify electrical synchrony and markedly improve clinical care of CRT patients. The first study will focus on using CRI to quantify how an adaptive device-based pacing algorithm improves electrical synchrony. The second study will evaluate the effect of native QRSd on the corresponding potential, or therapeutic window, of electrical resynchronization during LV-only pacing.

CHAPTER 3. ADAPTIVE CARDIAC RESYNCHRONIZATION THERAPY ALGORITHM AND ELECTRICAL SYNCHRONY

Adaptive Cardiac Resynchronization Therapy Algorithm and Electrical Synchrony

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SUMMARY

Background: The Adaptive cardiac resynchronization therapy (CRT) pacing algorithm (aCRT) has been shown to provide significant clinical benefit in heart failure patients. The effectiveness of aCRT optimization in reducing electrical dyssynchrony has not yet been well-characterized.

Methods: We studied 54 CRT patients programmed with aCRT, and measured electrical synchrony at multiple device settings. Electrical synchrony was quantified using a novel measure of wavefront fusion, cardiac resynchronization index (CRI), that analyzes areas between multiple pairs of anterior and posterior electrograms and calculates change in synchrony normalized to native rhythm.

Results: Programming using aCRT resulted in CRI of 62.3±4.1%; CRI at optimal setting (CRI_{OPT}) was significantly higher (89.5±1.1%, $p<0.001$). Patients optimized with LV-only aCRT pacing ($n=35$) had a significantly ($p<0.001$) greater CRI (75.8±2.5%) than patients optimized to biventricular (BiV) aCRT pacing ($n=19$) (37.3±7.8%). CRI with LV-only aCRT optimization was significantly higher than CRI at a standard BiV setting (53.5±4.3%, $p<0.001$), but significantly worse than the LV-only CRI_{OPT} setting (90.4±1.4%, $p<0.001$). The AVD at LV-only CRI_{OPT} was at least 20 milliseconds different than the AVD as optimized by the aCRT algorithm in 15 patients (42.9%). Patients optimized with BiV aCRT pacing had significantly lower CRI as compared to CRI_{OPT} (89.2±2.0%, $p<0.001$), which frequently required LV-only pacing, or BiV pacing with LV preactivation.

Conclusion: Electrical synchrony improvement is greater with LV-only aCRT optimization. Electrical synchrony can be improved in almost half of patients with LV-only aCRT pacing by optimizing the AVD. The majority of patients programmed with BiV aCRT pacing had optimal electrical synchrony by AVD optimization during LV-only pacing, or during sequential BiV pacing with LV preactivation.

Key words: Cardiac resynchronization therapy, Heart failure response, Electrocardiography, Electrical dyssynchrony, Body surface mapping

INTRODUCTION

Advancements with cardiac resynchronization therapy (CRT) pacemakers and defibrillators have been a tremendous breakthrough with reducing mortality rates (Bradley et al., 2003; Bristow et al., 2004), as well as improving symptoms (Cazeau et al., 2001; Young et al., 2003), left ventricular (LV) reverse remodeling,(Abraham et al., 2002; Higgins et al., 2003), and exercise capacity (Auricchio et al., 2002; Linde et al., 2002) in symptomatic heart failure (HF) patients with electrical dyssynchrony. Despite this record of success, approximately 30% of patients are non-responders, with minimal or no improvements in clinical and/or LV function (Auricchio & Prinzen, 2011). The underutilization of a standardized methodology to optimize CRT pacing setting and configurations is thought to be a prevailing cause of non-response (N. Varma et al., 2019).

Adaptive CRT (aCRT; Medtronic plc, Mounds View, MN) is a device pacing algorithm designed to improve response by minimizing right ventricular (RV) pacing in patients with normal atrioventricular (AV) node conduction, and by producing fusion with intrinsic activation via optimizing the atrioventricular delay (AVD) (Daoud & Houmsse, 2016; Krum et al., 2012). Safety and non-inferiority of aCRT versus echocardiographic optimization has previously been demonstrated (Martin et al., 2012). Subsequent analysis on aCRT report lower 30 day HF-associated and all-cause readmission rates (Starling et al., 2015), improved clinical response (Singh et al., 2013), and reduced incidence of atrial fibrillation (Birnie et al., 2017). However, to our knowledge, no research has yet assessed the effect of aCRT pacing on improving electrical synchrony.

Electrical synchrony has traditionally been measured by QRS duration (QRSd) narrowing using standard 12-lead electrocardiograms (ECG). However, QRSd has a number of well-known limitations (Auricchio & Yu, 2004; Engels et al., 2016; Molhoek et al., 2004; Mollema et al., 2007), including inconsistencies in reflecting mechanical dyssynchrony and delayed LV activation (Bleeker et al., 2004; Ghio et al., 2004; Kass, 2003; Mafi Rad et al., 2016), high interobserver variability (De Guillebon et al., 2010), and disagreements on how to define QRS width (De Pooter et al., 2016). Research in canine models of LBBB (Vernooy, Cornelussen, et al., 2007; Vernooy, Verbeek, et al., 2007), and later in humans (Sweeney et al., 2014), have demonstrated that improvements in electrical synchrony occur via fusion

between native and/or RV-paced (RVp) wavefronts moving posteriorly and leftward from the septum with LV-paced (LVp) electrical wavefronts moving anteriorly and rightward from the lateral or posterior wall of the LV. Such electrical wavefront fusion can be depicted not only by QRSd narrowing, but also by a frontal axis deviation shift, R wave emergence in anterior precordial leads, and/or reduced amplitudes in lateral leads (Sweeney et al., 2014; Sweeney et al., 2010). Our laboratory has shown that optimization of CRT programming based on the aforementioned markers of wavefront fusion are associated with improved systolic function (Gage et al., 2018). In the present study, the investigational ECG belt and a novel metric, called cardiac resynchronization index (CRI), were used to measure electrical synchrony (Bank et al., 2020). We have previously demonstrated that this measure of electrical synchrony accurately reflects wavefront fusion, and produces reproducible, physiologic, and dose-dependent changes concurrently with AVD and interventricular delay (VVD) optimization (Bank et al., 2020). The primary purpose of this study was to use CRI methodology to quantify the magnitude of improvement in electrical synchrony with aCRT.

METHODS

Study population

This was a retrospective analysis of 54 patients who received a Medtronic CRT pacemaker or defibrillator programmed with the aCRT algorithm. All patients were implanted for standard CRT indications and met the following inclusion criteria: LV ejection fraction (LVEF) ≤ 40%, New York Heart Association (NYHA) class II to ambulatory class IV HF, QRSd > 120 milliseconds, and on optimal medical therapy. Patients with less than 90% ventricular pacing, permanent atrial fibrillation, or right bundle branch block were excluded, but patients with non-specific interventricular conduction delay (IVCD) and complete heart block (CHB) were included. This study was approved by an Institutional Review Board (IRB), and all patients signed and gave informed consent.

AdaptivCRT™ algorithm

The aCRT algorithm provides ambulatory pacing optimization, based upon heart rate and native conduction (Daoud & Houmsse, 2016; Krum et al., 2012). For Viva™ CRT devices, the algorithm selects

LV-only pacing synchronized to intact RV conduction when both the heart rate is below 100 bpm and the atrial sensed-RV sensed (As-RVs) interval is less than 200 milliseconds (or the atrial paced-RV sensed [Ap-RVs] interval is less than 250 milliseconds). The algorithm provides BiV pacing during sinus tachycardia, irregular rhythm, and/or if either the As-RVs or Ap-RVs intervals are greater than 200 milliseconds and 250 milliseconds, respectively. For Claria™, Amplia™, Percepta™, and Serena™ CRT devices, the As-RVs and Ap-RVs thresholds that decipher between pacing configurations are 220 milliseconds and 270 milliseconds, respectively. During LV-only pacing, the AVD is optimized to either 70% of the As-RVs interval, or 40 milliseconds before the As-RVs interval, whichever interval is shorter. During BiV pacing, the AVD is either 30 milliseconds after the end of the P wave, or 50 milliseconds prior to the As-RVs interval. Interventricular delays are optimized as based on both the As-RVs interval, and the interval between sensing on the RV intracardiac electrogram to the end of the QRS complex on a far-field channel (i.e., RVs-QRSend) (Krum et al., 2012). If intrinsic QRSd is greater than 160 milliseconds, then the aCRT algorithm will administer simultaneous BiV pacing (Daoud & Houmsse, 2016).

Data Acquisition Protocol

A device interrogation assessing percent atrial and ventricular pacing, arrhythmia burden, lead thresholds, and the As-RVs interval, was performed. Standard 12-lead ECGs and ECG belt data were collected with inhibiting CRT pacing (i.e., native), and at the baseline programmed aCRT device setting. In patients with CHB, RVp rhythm was used in place of native conduction. Patients had ECG belt data acquired with simultaneous BiV and LV-only pacing over a wide range of AVDs. Patients also had data acquired with VVD optimization, typically ranging from LV preactivation of 60 milliseconds, to RV preactivation of 20 milliseconds.

Data was acquired using 1 of 2 investigational ECG belt systems. Both investigational ECG belt systems consisted of unipolar leads distributed over the anterior and posterior upper torso. One version of the ECG belt system (n=52) had 17 anterior and 36 posterior unipolar ECG electrodes (Verathon Inc, Bothell, WA; modified by Medtronic, Mounds View, MN) (Bank et al., 2018; Gage et al., 2017; Johnson et al., 2017). The other ECG belt system (n=2) had 20 anterior and 20 posterior unipolar ECG electrodes

(Medtronic ECG Belt Research System ver. 2.0, Medtronic, Mounds View, MN). An ECG amplifier with a storage unit for both ECG belt versions was used.

Measurement of Electrical Dyssynchrony

Data was analyzed via an off-line proprietary post-processing software algorithm (MATLAB version 7.0, MathWorks, Inc., Natick, MA) (Bank et al., 2020; Curtin et al., 2018). Briefly, the algorithm calculated the average paired difference between areas under multiple pairs of anterior and posterior curves (AUC) for a single heartbeat. Three beats were averaged for each acquired device pacing setting. The calculated AUC was defined as negative when the area encompassed by negatively deflected anterior electrodes was greater than that encompassed by positive posterior electrodes, which was indicative of an electrical wavefront that traverses posteriorly. Electrical synchrony, quantified as CRI, was calculated as the percent change in AUC at any device setting normalized to native rhythm, or RVp in patients with CHB (Bank et al., 2020). CRI_{OPT} was defined as the CRT pacing setting that resulted in the highest CRI value. LV-only CRI_{OPT} was defined as the device setting with the highest CRI value during LV-only pacing. BiVVV0 CRI_{OPT} represented the pacing setting with the highest CRI achieved during simultaneous BiV pacing. BiV CRI_{OPT} was the optimal biventricular pacing setting, either simultaneous or with an interventricular delay, with the highest CRI value. Standard BiV was defined as simultaneous biventricular pacing at an AVD that was 70% of intrinsic PR interval

Statistical analysis

IBM SPSS Statistics 23 (IBM Corp. Released 2016, IBM SPSS Statistics for Windows, Version 23, Armonk, NY: IBM Corp) was used for statistical analysis. Continuous variables were presented as mean ± standard error (SE), and categorical variables as counts (percentages). A one-way analysis of variance (ANOVA) and a chi-square assessed differences in adaptive pacing configurations (i.e., LV-only aCRT versus BiV aCRT) with regard to clinical (e.g., age, LVEF) and demographic characteristics (e.g., NYHA HF class, QRS morphology), respectively. A repeated measures ANOVA with Bonferroni post-hoc

tests were used to compare within-patient differences in CRI values across various device pacing configurations.

RESULTS

Patient population

Table 1 summarizes the baseline characteristics of the 54 patients studied. The majority of patients (n=50, 92.6%) had ECG belt data acquired within three weeks following their CRT implant (mean±SE: 10.7±1.3 days). Average native QRSd was 143.4±3.2 milliseconds, LVEF was 26.6±1.0%, and 40 (74.1%) patients had a LBBB QRS morphology. Patients were on good medical therapy, with 88.9% of the cohort on an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB), and 88.9% on a beta-blocker. Left ventricular lead position was predominantly lateral (n=32, 59.3%) or posterolateral (n=17, 31.5%).

In the total patient cohort, aCRT pacing significantly reduced QRSd (p<0.001). Patients optimized to LV-only aCRT pacing differed from those programmed to BiV aCRT pacing, as shown in Table 1. There was a higher percentage of patients optimized to BiV aCRT pacing that were male (p=0.005), had ischemic cardiomyopathy (p=0.007), and had RVp as their underlying rhythm. A lower percentage of BiV aCRT patients had an underlying LBBB. As expected, BiV aCRT patients had longer PR intervals and a higher percentage of first degree AV block (p<0.001). There were no significant differences in native QRSd between patients optimized to LV-only versus BiV aCRT pacing (p=0.431). Conversely, significant reductions in QRSd were observed in patients with LV-only aCRT pacing (141.5±3.5 milliseconds vs. 97.4±3.3 milliseconds, p<0.001), but not with BiV aCRT pacing (p=0.766). The percent electrical resynchronization, as measured by CRI, was significantly (p<0.001) higher in patients optimized to LV-only aCRT pacing (76.2±2.7%) compared to BiV aCRT pacing (37.3±7.8%). CRI during aCRT pacing (62.5±4.1%) in the total cohort of patients was significantly lower than the CRI at the CRI_{OPT} pacing setting (89.5±1.1%, p<0.001).

Patients optimized by AdaptivCRT™ to LV-only pacing

Figure 1 shows native 12-lead ECGs (A), and also CRI (B) and ECG belt electrograms (C) acquired at different AVDs during simultaneous BiV and LV-only pacing in a patient optimized to LV-only aCRT. The patient had LBBB conduction; ventricular activation using ECG belt technology showed delayed LV activation during native rhythm, with a dominant wavefront moving posteriorly, as evidenced by positive and negative deflections in the posterior and anterior electrograms, respectively. Simultaneous BiV pacing at AVDs between 100 and 180 milliseconds resulted in CRI values that ranged from 50.8% to 62.1%. Electrograms at these settings exhibited reduced amplitude of both anterior and posterior waveforms as compared to native rhythm, representing improved electrical synchrony due to electrical cancellation from opposing wavefronts. Still, the RVp wavefront exerted a greater contribution to ventricular fusion than the LVp wavefront, depicted by the disproportionately larger amplitude of the negatively deflected anterior electrograms that occurred irrespective of optimizing the AVD. Atrial-synchronized LV-only pacing at a short AVDs (e.g., 100 milliseconds) resulted with reduced amplitude and reversed polarity of anterior and posterior waveforms as compared to native, with the dominant wavefront moving anteriorly as a result of a prevailing LVp wavefront that preceded the native wavefront. The highest CRI value during LV-only pacing occurred by lengthening the AVD to 120 milliseconds. Improved electrical synchrony at this pacing configuration was observed by the smallest amplitudes of anterior and posterior electrograms, owning to improved fusion between the timing of the LVp and native wavefronts. As the AVD increased beyond 120 milliseconds, the native wavefront progressively preceded the LVp wavefront, as shown by greater amplitude of the anterior and posterior waveforms with morphology gradually approaching that of the native LBBB morphology. Ventricular activation and CRI values were nearly identical during BiV and LV-only pacing at AVDs of 180 and 200 milliseconds, demonstrating that ventricular fusion was predominately composed of fusion between the LVp and native wavefront, with minimal contribution from the RVp wavefront. In this patient, the AVD at the CRI_{OPT} setting was 20 milliseconds shorter than the AVD during LV-only aCRT optimization, resulting in an improvement in electrical resynchronization from 82.1% to 92.2%.

Figure 2 shows 12-lead ECGs during native rhythm (A), and also CRI (B) and electrograms (C) during simultaneous BiV and LV-only pacing at AVDs between 60 and 120 milliseconds, in a patient with native LBBB conduction. The CRI_{OPT} setting occurred at an AVD 10 milliseconds shorter than the optimized AVD by the LV-only aCRT algorithm, with an improvement in electrical resynchronization from 77.0% to 92.3%. Depicted in Figure 3 is another example of a LBBB patient optimized to LV-only aCRT pacing. CRI (3B) and electrograms (3C) were acquired during BiV pacing at an AVD of 120 milliseconds, and also during LV-only pacing between AVDs of 60 and 180 milliseconds. In this patient, the AVD at CRI_{OPT} was 30 milliseconds shorter compared to the optimized AVD by the aCRT pacing algorithm, resulting in an improvement in electrical resynchronization from 51.5% to 89.0%.

Thirty-five patients (64.8%) were optimized to LV-only aCRT pacing. Figure 4A shows a histogram of differences in AVD chosen by the two methodologies. In 6 (17.1%) of the 35 patients, the AVD during aCRT optimization was the same as the AVD at the CRI_{OPT} pacing setting. In an additional 14 (40.0%) patients, the AVD optimized by aCRT was either 10 milliseconds shorter or 10 milliseconds longer than the AVD chosen by CRI_{OPT}. In 15 (42.9%) patients, the AVD was at least 20 milliseconds different between the two methodologies. The average AVD optimized by aCRT pacing was significantly longer than the AVD at the CRI_{OPT} setting (121.4±3.7 milliseconds vs. 109.7±5.2 milliseconds, $p<0.001$). There were significant differences in CRI between different pacing configurations ($p<0.001$) (Figure 4B). CRI during LV-only aCRT pacing (76.2±2.7%) was significantly ($p<0.001$) greater than the CRI at standard BiV (53.6±4.2%), but not significantly different ($p=0.080$) than optimal simultaneous BiV pacing (64.6±4.3%). The CRI during LV-only aCRT pacing was significantly lower ($p<0.001$) than the CRI measured at LV-only CRI_{OPT} (90.4±1.4%).

Patients optimized by AdaptivCRT™ to BiV pacing

Figure 5 shows 12-lead ECGs of native conduction (A), and CRI (B) and ventricular activation (C) for a LBBB patient that was programmed to BiV aCRT. The aCRT algorithm selected simultaneous BiV pacing an AVD of 100 milliseconds, which resulted in a CRI of 49.5%. The CRI during BiV aCRT optimization was lower than the CRI at the optimal simultaneous BiV setting (59.7% at AVD of 120

milliseconds), CRI at the optimal LV-only setting (82.1% at AVD of 140 milliseconds), and CRI at the optimal sequential BiV setting (82.7% at VVD delay of 20 milliseconds with a sensed AVD of 100 milliseconds). Improved electrical synchrony and ventricular fusion occurred with 20 milliseconds of LV preactivation since, during simultaneous BiV pacing, RVp and/or native wavefronts preceded the LVp wavefront. Figure 6 shows CRI (A) and electrograms (B) for a patient with CHB and optimized with simultaneous BiV pacing at a paced AVD of 170 milliseconds. RVp rhythm was used in place of native, which resembled LBBB morphology with a posteriorly-moving wavefront. CRI at the aCRT setting was 63.3%, and was characterized by a dominant RVp wavefront with minimal fusion from the LVp wavefront. As the LV lead was progressively preactivated to 30 milliseconds, CRI improved and reached 94.7% electrical resynchronization. CRI decreased with further LV preactivation, due to the a dominant wavefront moving anteriorly from the LV lead that preceded the RVp wavefront.

Of the 19 patients optimized to BiV aCRT pacing, the majority (n=14, 73.6%) were paced simultaneously. There were 4 patients paced sequentially via the aCRT algorithm, with LV preactivation of 20 milliseconds and 10 milliseconds in 1 and 3 patients, respectively. The mean LV preactivation was -12.5±2.2 milliseconds. Another patient sequential pacing, but with RV preactivation by 10 milliseconds. There were significant differences in CRI with different pacing confirmations ($p<0.001$). CRI_{OPT} (88.1±1.9%) occurred with simultaneous BiV pacing in 5 patients, sequential BiV pacing in 8 patients (mean LV preactivation: -34.3±6.1 ms), and LV-only pacing in 6 patients. As shown in Figure 7, the CRI during aCRT pacing (37.3±7.8%) was not significantly different than CRI during standard simultaneous BiV pacing (46.3±9.7%, $p=0.101$). However, CRI during BiV aCRT optimization was significantly lower than the CRI at the optimal biventricular setting, including either simultaneous or sequential pacing (69.6±5.5%, $p=0.001$). Electrical resynchronization during BiV aCRT optimization was also significantly lower than the LV-only CRI_{OPT} setting (83.2±2.3, $p=0.002$), and as well as at the best overall CRI_{OPT} setting (89.2±2.0%, $p<0.001$).

DISCUSSION

Novel technology that quantifies cardiac electrical synchrony, as based on the concepts of wavefront fusion and cancellation, was used in this retrospective analysis to assess the effect of the aCRT algorithm on improvements with electrical resynchronization. Electrical resynchronization, as measured by CRI, was improved by 62.3±4.0% in patients with LBBB, IVCD, or RVp rhythm treated with CRT for standard indications and programmed via the aCRT algorithm. Electrical synchrony can be significantly improved to 89.5±1.1% ($p<0.001$) using the novel methodology derived from ECG belt technology. Patients optimized to LV-only aCRT pacing had a significantly greater improvement in CRI (75.8±2.5%), as compared to those optimized with BiV aCRT pacing (37.3±7.8%, $p<0.001$). In patients with LV-only aCRT, pacing at the optimized AVD resulted in significantly better electrical synchrony than simultaneous BiV pacing at a standard AVD, but significantly worse electrical synchrony than at the CRI_{OPT} AVD during LV-only pacing. Over 40% of patients with LV-only aCRT pacing were optimized to an AVD that was at least 20 milliseconds different from the AVD at CRI_{OPT}. In patients optimized to BiV pacing by aCRT, a marked improvement in electrical synchrony was achieved, frequently via LV preactivation or LV-only pacing. We propose that aCRT pacing optimization produces its beneficial effects predominantly through selection of LV-only pacing at an AVD that results in effective electrical wavefront fusion and cancellation. Electrical synchrony can be further improved in patients programmed to LV-only pacing by optimizing AVD. The majority of patients programmed to BiV aCRT pacing exhibited superior improvements in electrical synchrony by either changing pacing configurations to LV-only, or to a sequential BiV paced setting with optimal LV preactivation.

Measurement of electrical synchrony using CRI

This ECG belt methodology described in this paper involved a proprietary algorithm that analyzed anterior and posterior electrograms for evidence of wavefront fusion and electrical cancellation (Bank et al., 2020; Curtin et al., 2018). Changes in electrogram width, amplitude and polarity corresponded with changes in the paired difference between the anterior and posterior area under the electrograms. By normalizing AUC values at any programmed setting to native conduction, the percent electrical

resynchronization for a given patient can be determined and quantified as CRI. Previous research has showed that changes in pacing configurations, as well as optimizing the timing of the AVD and VVDs, produces characteristic changes in CRI, of which can be explained and predicted based on the concept of electrical wavefront fusion (Bank et al., 2020).

LV-only vs simultaneous BiV pacing

Previous studies have demonstrated improved acute hemodynamics (Lee et al., 2007; van Gelder et al., 2005; C. Varma et al., 2003), and echocardiographic LV function (Gage, Burns, Vatterott, Kubo, & Bank, 2012), with appropriately timed LV-only pacing as compared to BiV pacing. While preliminary research on aCRT optimization reported non-inferiority with improving clinical outcomes as compared to echocardiographic optimization, post-hoc analysis report superiority of LV-only aCRT with improving a clinical composite score (Martin et al., 2012), reducing hospitalization and mortality rates (Birnie, Lemke, et al., 2013), and reducing atrial fibrillation incidence (Hsu et al., 2019). In patients with normal AV conduction, LV-only aCRT pacing resulted in better regional (apical, septal and anteroseptal) and global LV systolic function than BiV aCRT pacing (Burns et al., 2017). In contrast, multi-center clinical trials have generally shown no major differences in clinical and echocardiographic outcomes with LV-only versus BiV pacing (Boriani et al., 2010; Gasparini et al., 2006; Rao et al., 2007; Skaf et al., 2017). A major deficiency of these larger clinical trials is that device optimization was either not performed, or were performed with methods that have major limitations. In contract, the aCRT algorithm is specifically designed to optimize device programming by providing RV-synchronized, LV-only pacing in CRT patients with normal AV conduction.

In the present study, patients optimized by aCRT to LV-only pacing achieved greater improvements in electrical synchrony than those optimized to BiV pacing. Such differences in improvements in electrical synchrony between LV-only and BiV aCRT pacing configurations can be explained by the physiologic timing of right-sided and left-sided wavefronts that are necessary to produce optimal fusion. Atrial-synchronized LV-only pacing, in the majority of patients, allows for improved electrical fusion of right-sided and left-sided wavefronts with AVD optimization. In particular, we

previously showed that LV-only pacing produces dose-dependent and physiologic changes in CRI in 70 patients, with an average of 89.6% electrical resynchronization (Bank et al., 2020). In contrast, AVD optimization during BiV pacing typically elicits trivial changes in electrical resynchronization, with CRI infrequently improving significantly with prolonging the AVD (Figure 1, 2, 5).

Assessment of the timing between RVp and LVp wavefronts can be made during BiV pacing in patients with CHB, of which are the subset of HF patients that have no native conduction to fuse with paced ventricular wavefronts. Additionally, owning to the fact that native contribution in negligible to ventricular fusion during short AVDs, timing of the RVp and LVp wavefronts can be assessed in patients with intact AV conduction by programming the CRT device at short AVDs. The AUC during simultaneous BiV pacing is negative in the vast majority of patients with intact native conduction, demonstrating imbalanced ventricular fusion that is attributable from a dominant RVp wavefront that moves posteriorly (Bank et al., 2020). The native wavefront increasingly contributes with subsequent lengthening of the AVD during simultaneous BIV pacing and, owning the principle of wavefront summation, will cause decrements in fusion with the LVp wavefront by constructively reinforcing the posteriorly-moving RVp wavefront. This finding helps explain why previous studies assessing methodologies to optimize AVD during simultaneous BiV pacing have not shown benefit (Abraham et al., 2010; Ellenbogen et al., 2010). In contrast, during LV-only pacing and among patients with intact AV node conduction, ventricular fusion is composed solely of the native and LVp wavefronts. LV-only pacing at a short AVD will consistently cause the LVp wavefront to precede native conduction (Bank et al., 2020). Progressive improvement in electrical resynchronization occurs with lengthening the AVD until an optimum is reached, after which decrements in ventricular fusion are attributable to a dominant native wavefront that precedes the LVp wavefront.

The aCRT algorithm selects BiV pacing for patients with prolonged AV conduction. Our analysis suggests that this selection of patients for BiV pacing may not beneficial, as long as patients have intact AV node conduction. Patients with prolonged AV conduction exhibit similar relationship between CRI and AVD optimization during LV-only pacing as compared to patients in sinus rhythm and normal AV conduction (Figure 5). The notable difference is that, in patients with prolonged AV conduction, the CRI_{OPT} setting occurs at a longer AVD as a result of slower native conduction. Therefore, patients with intact but

prolonged AV conduction optimized to BiV aCRT pacing may exhibit improved resynchronization with either LV-only pacing at the best AVD, or with sequential BiV pacing with optimal LV preactivation.

Clinical significance

The predominant mechanism of action of CRT is to improve intraventricular LV synchrony (Engels et al., 2016; Nguyen et al., 2018; Sweeney et al., 2014). This occurs through fusion of electrical wavefronts emanating from native conduction, and both RVp and LVp wavefronts. Previous research in canine models observed that, owning to slow transseptal conduction, simultaneous BiV fusion does not result with optimal fusion between RVp and LVp wavefronts (Strik, van Deursen, et al., 2013). Instead, improved wavefront fusion was achieved with LV preactivation during sequential BiV pacing. Improvements in electrical and hemodynamic synchrony in canine models of LBBB have been shown to exhibit stimulus-response curves during BiV and LV-only pacing, similar to that as observed in this analysis (Strik, van Middendorp, et al., 2013). Human studies have reported associations between improved electrical resynchronization with subsequent improved echocardiographic response. Sweeney demonstrated that increased R wave amplitude in V1 and V2, anteriorly propagating depolarization, and right-axis frontal deviation shift on 12-lead ECGs indicate improved ventricular wavefront fusion, and were associated with increased probability of LV-reverse remodeling (Sweeney et al., 2014). We recently demonstrated that optimization of CRT programming using 12-lead ECG markers of wavefront fusion resulted in significantly improved LV size and systolic function, particularly in patients with intramyocardial fibrosis (ischemic or non-ischemic) (Gage et al., 2018). Such results are highly supportive that improvements in LV reverse remodeling occur from improved electrical resynchronization and ventricular fusion between the native and paced wavefronts during CRT pacing.

Limitations

This study utilized a new methodology for measuring electrical dyssynchrony. This methodology offers a number of advantages over other methods for CRT optimization, including ease of use, practicality, noninvasive nature, automation, and high sensitivity with regard to detecting dose-dependent and

physiologic changes in electrical resynchronization with different pacing configurations. Despite these advantages, it is difficult to demonstrate superiority of this methodology in measuring electrical synchrony as compared to others, as there is no gold standard. Patients were studied at rest and, thus, we cannot address the effects of aCRT during activity when automatic adjustments in programming occur with this algorithm. This was also a retrospective analysis in a modest number of patients at a single time point early after CRT placement. The main limitation of our study is that patients were not prospectively programmed based on our assessment of electrical synchrony. Thus, we cannot evaluate causality between CRI and superior clinical and/or echocardiographic outcomes as compared to standard programming, or to aCRT optimization. Future prospective randomized studies are planned to assess clinical and echocardiographic outcomes as a result of CRT optimization with this methodology.

CONCLUSION

A novel quantitative methodology, as based on the principles of wavefront fusion and cancellation, and the investigational ECG belt system were used to measure electrical synchrony in HF patients programmed with the aCRT pacing algorithm. We show ~75% and ~37% electrical resynchronization with LV-only aCRT and BiV aCRT optimization, respectively. LV-only pacing via the aCRT algorithm resulted in superior improvements in cardiac electrical synchrony than standard BiV pacing, of which may explain the reason for its demonstrable benefit in previous studies. However, improvements in electrical synchrony can be achieved in over 40% of patients programmed LV-only by optimizing the AVD. The majority of patients optimized to BiV aCRT pacing had improved electrical synchrony by programming appropriately timed LV-only pacing, or sequential BiV pacing with LV preactivation.

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ABBREVIATIONS

ACEI = Angiotensin-converting enzyme inhibitor

aCRT = Adaptive CRT

Ap-RVs = Atrial-paced RV sensed interval

ARB = Angiotensin-receptor block

As-RVs = Atrial-sensed RV sensed interval

AUC = Area under the curves

AV = Atrioventricular

AVD = Atrioventricular delay

BiV = Biventricular

CHB = Complete heart block

CRI = Cardiac resynchronization index

CRT = Cardiac resynchronization therapy

ECG = Electrocardiogram

HF = Heart failure

IRB = Institutional Review Board

IVCD = Interventricular conduction delay

LBBB = Left bundle branch block

LV = Left ventricle

LVEF = Left ventricular ejection fraction

LVESV = Left ventricular end-systolic volume

LVp = LV-paced

NYHA = New York Heart Association

QRSd = QRS duration

RV = Right ventricle

RVp = RV-paced

VVD = Interventricular delay

AUTHOR CONTRIBUTIONS

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Funding secured by: Dr. Bank, Dr. Burns

Data collection: Dr. Bank, Dr. Burns

Data analysis/interpretation: Dr. Bank, Ms. Harbin

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Drafting article: Ms. Harbin

Critical revision of article: All authors

Approval of article: All authors

TABLE LEGENDS

Table 1. Cohort demographics and anthropometrics.

TABLES

Table 1. Cohort demographics and anthropometrics.

	Total (*n*=54)	**LV-only (*n*=35)**	**BiV (*n*=19)**	***p*-value**
Male (%)	35 (64.8)	18 (51.4)	17 (89.4)	0.005
Age (years)	68.1±1.6	65.7±2.0	72.6±2.3	0.036
Ejection fraction (%)	26.8±1.0	26.2±1.4	27.8±1.5	0.451
LV end systolic volume (mL)	130.8±6.9	131.9±9.5	128.5±9.2	0.816
LV end diastolic volume (mL)	176.7±7.8	176.1±10.4	178.1±11.6	0.991
NYHA Class (*n*[%])				
II	17 (31.4)	11 (31.4)	6 (31.5)	0.774
III	37 (68.5)	24 (68.5)	13 (68.4)	
Ischemic cardiomyopathy (*n*[%])	21 (38.9)	9 (25.7)	12 (63.2)	0.007
QRS morphology (*n*[%])				
LBBB	40 (74.1)	30 (85.7)	10 (52.6)	<0.008
IVCD	12 (22.2)	5 (14.3)	7 (36.8)	
RV-paced LBBB	2 (3.7)	0 (0)	2 (10.5)	
Native QRS duration (milliseconds)	143.4±3.2	141.5±3.5	146.8±6.3	0.431
Native PR interval (milliseconds)	197.3±5.1	179.3±3.6	232.4±8.6	<0.001
1st degree AV block (*n*[%])	19 (35.2)	3 (8.5)	16 (84.2)	<0.001
RV lead (*n*[%])				
Apical	13 (24.1)	8 (22.9)	5 (26.3)	0.776
Septal	41 (75.9)	27 (77.1)	14 (73.7)	
LV lead (*n*[%])				
Anterior	2 (3.7)	1 (2.6)	1 (6.3)	0.460
Anterolateral	3 (5.6)	1 (2.6)	2 (12.5)	
Lateral	32 (59.3)	20 (57.1)	10 (62.5)	
Posterolateral	17 (31.5)	13 (37.1)	3 (18.8)	
ACEI/ARB (*n*[%])	48 (88.9)	34 (97.1)	14 (73.6)	0.009
Beta blockers (*n*[%])	48 (88.9)	34 (97.1)	14 (73.6)	0.009
Digoxin (*n*[%])	6 (11.1)	5 (14.2)	1 (5.3)	0.314
aCRT QRSd (milliseconds)	115.4±4.3	97.4±3.3	148.6±4.5	<0.001
aCRT CRI (%)	62.5±4.1	76.2±2.7	37.3±7.8	<0.001

Mean ± standard error (SE).
Categorical variables are expressed as count (% within column).
Differences for continuous and categorical variables were assessed by a one-way analysis of variance (ANOVA) and a chi-squared test, respectively.
Abbreviations: ACEI, angiotensin converting enzyme inhibitor; aCRT; Adaptive CRT; ARB, angiotensin receptor II blocker, AV, atrioventricular; BiV, biventricular, BMI, body mass index; LBBB, left bundle branch block, LV, left ventricle; IVCD, Inter-ventricular conduction delay; NYHA, New York Heart Association; RV, right ventricle.

FIGURE LEGENDS

Figure 1. ECG belt electrograms for an aCRT LV-only patient in normal sinus rhythm with a LBBB

Native 12-lead ECGs (A), and ECG belt CRI (B) and electrograms (C) during simultaneous BiV and LV-only pacing in a 46-year-old female with intact AV conduction. Abbreviations: aCRT, Adaptive CRT; AVD, atrioventricular delay; BiV, Biventricular; CRI, Cardiac resynchronization index; LV, Left ventricle.

Figure 2. ECG belt electrograms for an aCRT LV-only patient in normal sinus rhythm with a LBBB

Native 12-lead ECGs (A), and ECG belt CRI (B) and electrograms (C) during BiV and LV-only pacing in a 64-year-old male with intact AV conduction. Abbreviations: aCRT, Adaptive CRT; AVD, Atrioventricular delay; BiV, Biventricular; CRI, Cardiac resynchronization index; LV, Left ventricle.

Figure 3. ECG belt electrograms for an aCRT LV-only patient in normal sinus rhythm with a LBBB

Native 12-lead ECGs (A), and ECG belt CRI (B) and electrograms (C) during simultaneous BiV and LV-only pacing in a 79-year-old male with intact AV conduction. Abbreviations: aCRT, Adaptive CRT; AVD, Atrioventricular delay; BiV, Biventricular; CRI, Cardiac resynchronization index; LV, Left ventricle.

Figure 4A. Absolute difference in atrioventricular delays between the aCRT LV-only algorithm and LV-only CRI_{OPT} (*n*=35)

Data presented as counts. Absolute difference was calculated as the difference between the AVD at the CRI_{OPT} pacing setting minus the AVD at the aCRT pacing setting. A negative difference indicates CRI methodology chose a shorter AVD compared to aCRT, while a difference of zero indicates that both CRI methodology and the LV-only aCRT algorithm selected the same AVD. Abbreviations: AVD, Atrioventricular delay

Figure 4B. Electrical synchrony among patients with aCRT LV-only pacing (*n*=35)

Individual CRI values presented, with group mean and 95% confidence interval. *Denotes significantly different CRI compared to CRI with LV-only aCRT pacing (p<0.05). Abbreviations: aCRT, Adaptive CRT; AVD, Atrioventricular delay; BiVVV0, Simultaneous biventricular, CRI, Cardiac resynchronization index; CRI, Cardiac resynchronization index; LV, Left ventricle.

Figure 5. ECG belt electrograms for an aCRT BiV patient with a first-degree AV block and a LBBB Native 12-lead ECGs (A), and ECG belt CRI (B) and electrograms (C) during BiV and LV-only pacing in a 72-year-old male with a first-degree AV block.

Interventricular delays were collected in 20 millisecond intervals, and at a sensed AVD of 100 milliseconds. Abbreviations: aCRT, Adaptive CRT; AVD, Atrioventricular delay; BiV, Biventricular; CRI, Cardiac resynchronization index; VVD, Interventricular delay

Figure 6. Interventricular delay optimization and ECG Belt electrograms for a patient with complete heart block and optimized to aCRT BiV pacing

ECG Belt CRI (A) and electrograms (B) in a 62-year-old man with CHB Interventricular delays were collected in 10 millisecond intervals, and at a paced AVD of 170 milliseconds. Abbreviations: CRI, cardiac resynchronization index; RV, right ventricle; VVD, interventricular delay

Figure 7. Electrical synchrony in patients with aCRT BiV pacing (n=35)

Mean±SE. *Denotes significantly different CRI compared to CRI with LV-only aCRT pacing (p<0.05).

FIGURES

Figure 1. ECG belt electrograms for an aCRT LV-only patient in normal sinus rhythm with a LBBB

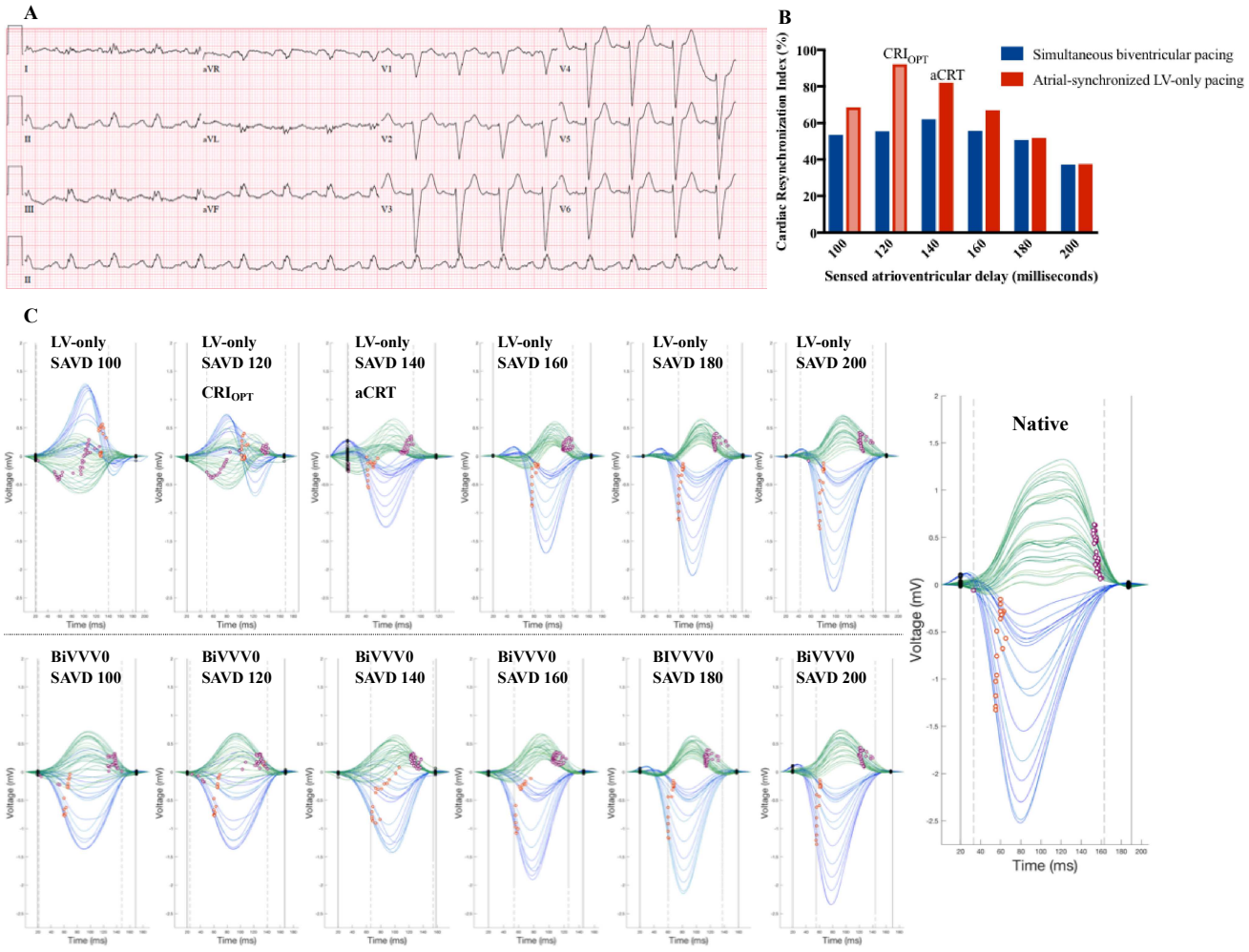


Figure 2. ECG belt electrograms for an aCRT LV-only patient in normal sinus rhythm with a LBBB

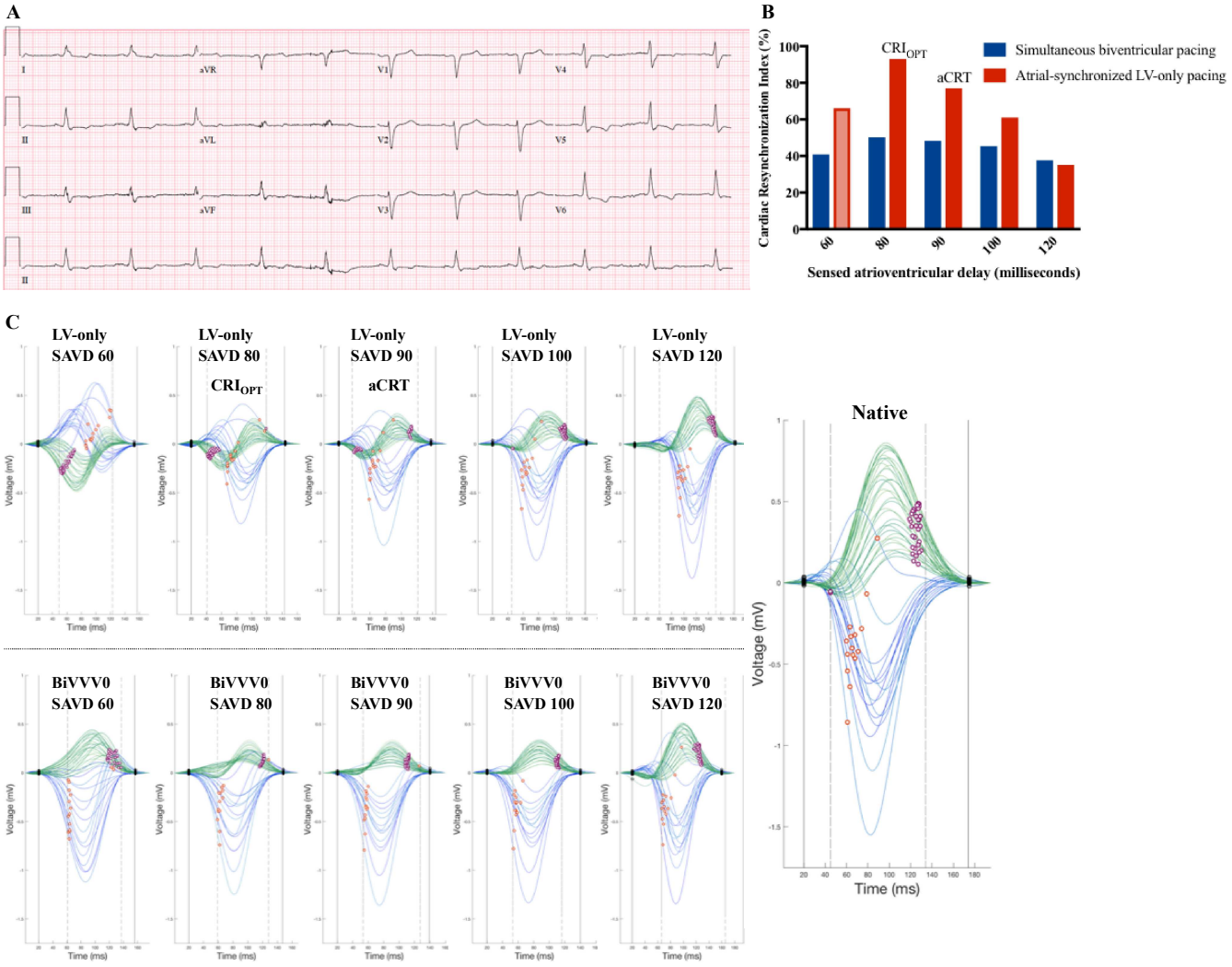


Figure 3. ECG belt electrograms for an aCRT LV-only patient in normal sinus rhythm with a LBBB

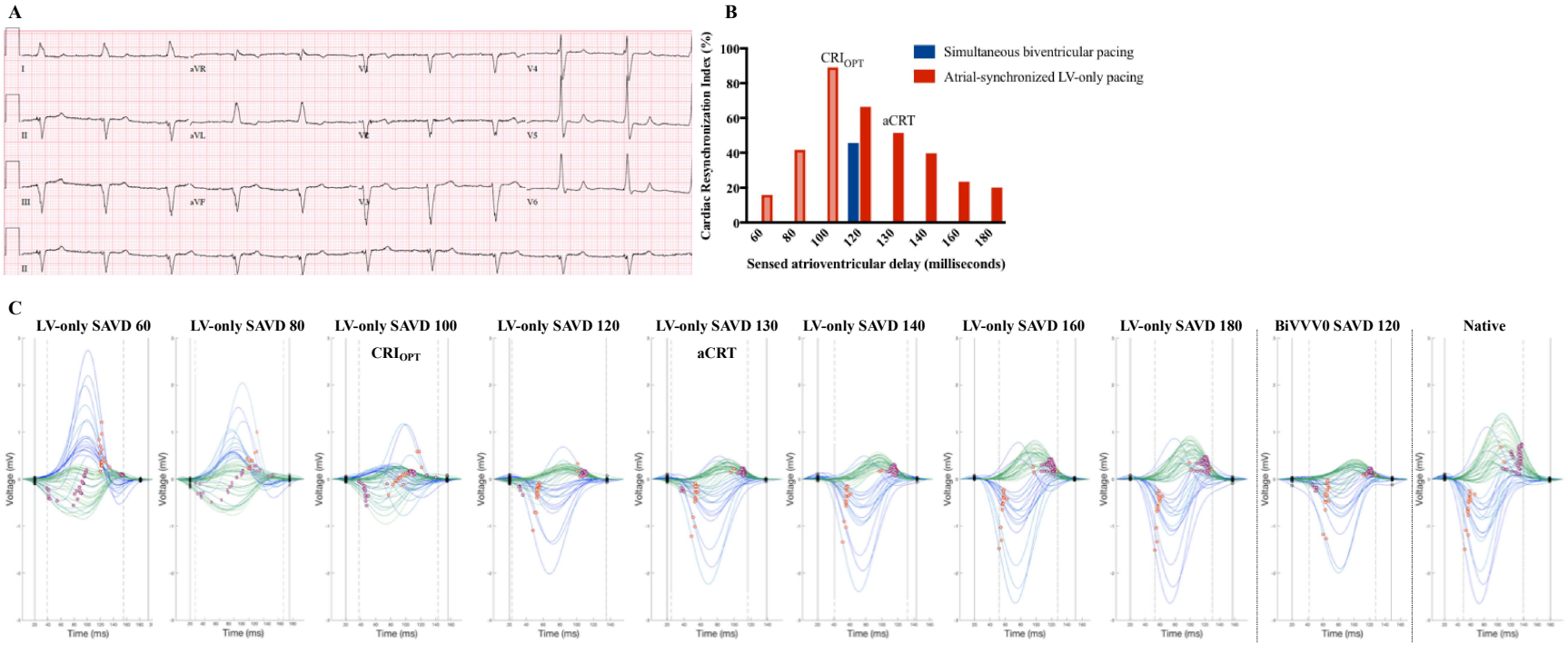


Figure 4A. Absolute difference in atrioventricular delays between the aCRT LV-only algorithm and LV-only CRI_{OPT} (n=35)

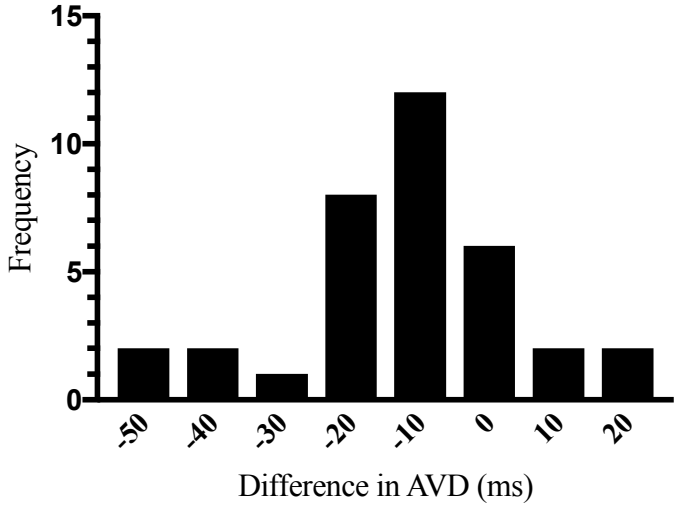


Figure 4B. Electrical synchrony among patients with aCRT LV-only pacing (*n*=35)

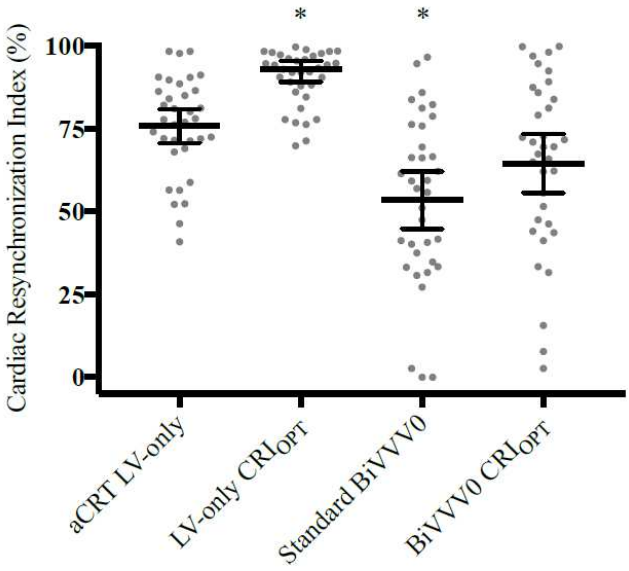


Figure 5. ECG belt electrograms for an aCRT BiV patient with a first-degree AV block and a LBBB

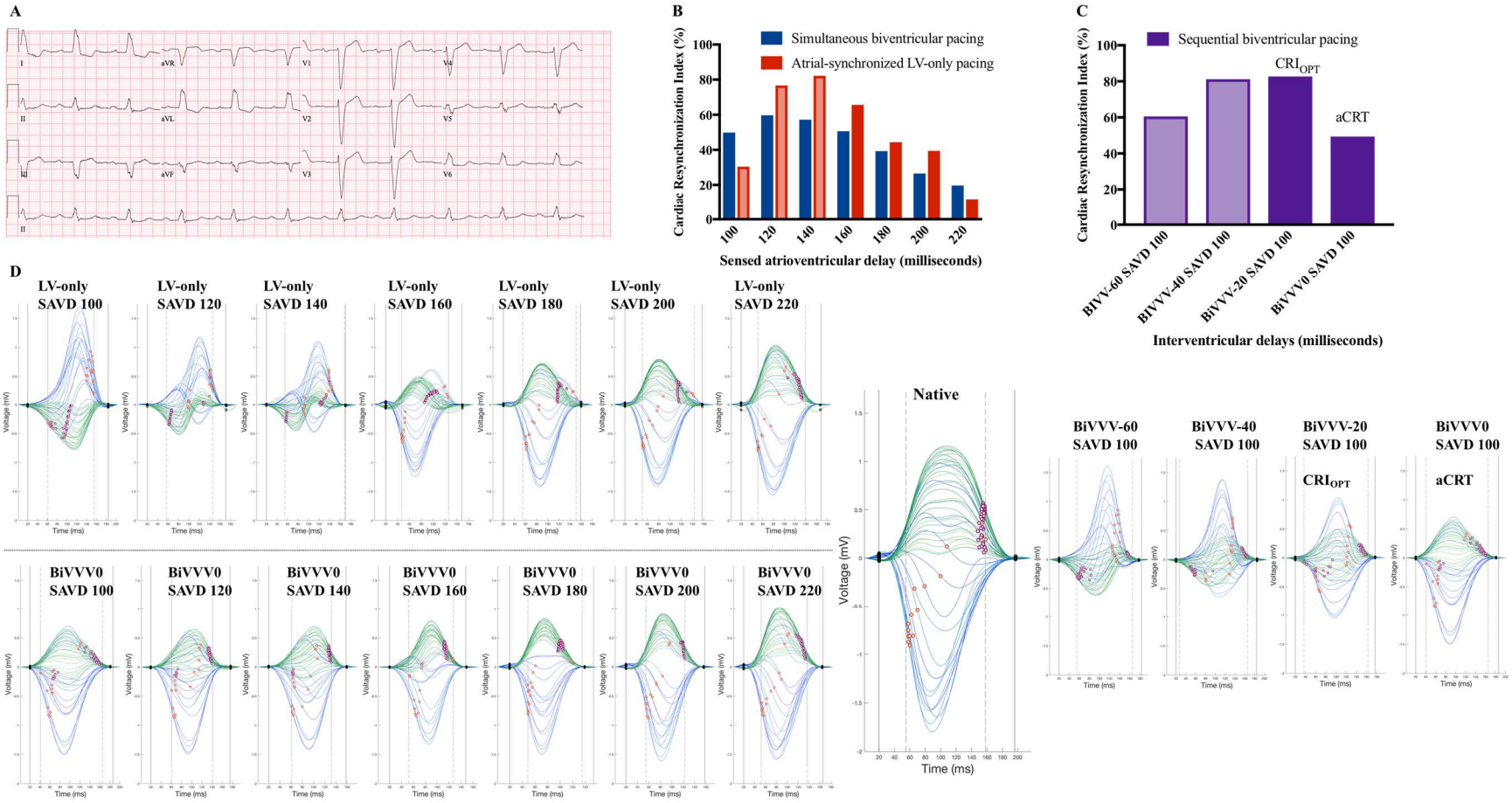


Figure 6. Interventricular delay optimization and ECG Belt electrograms for a patient with complete heart block and optimized to aCRT BiV pacing

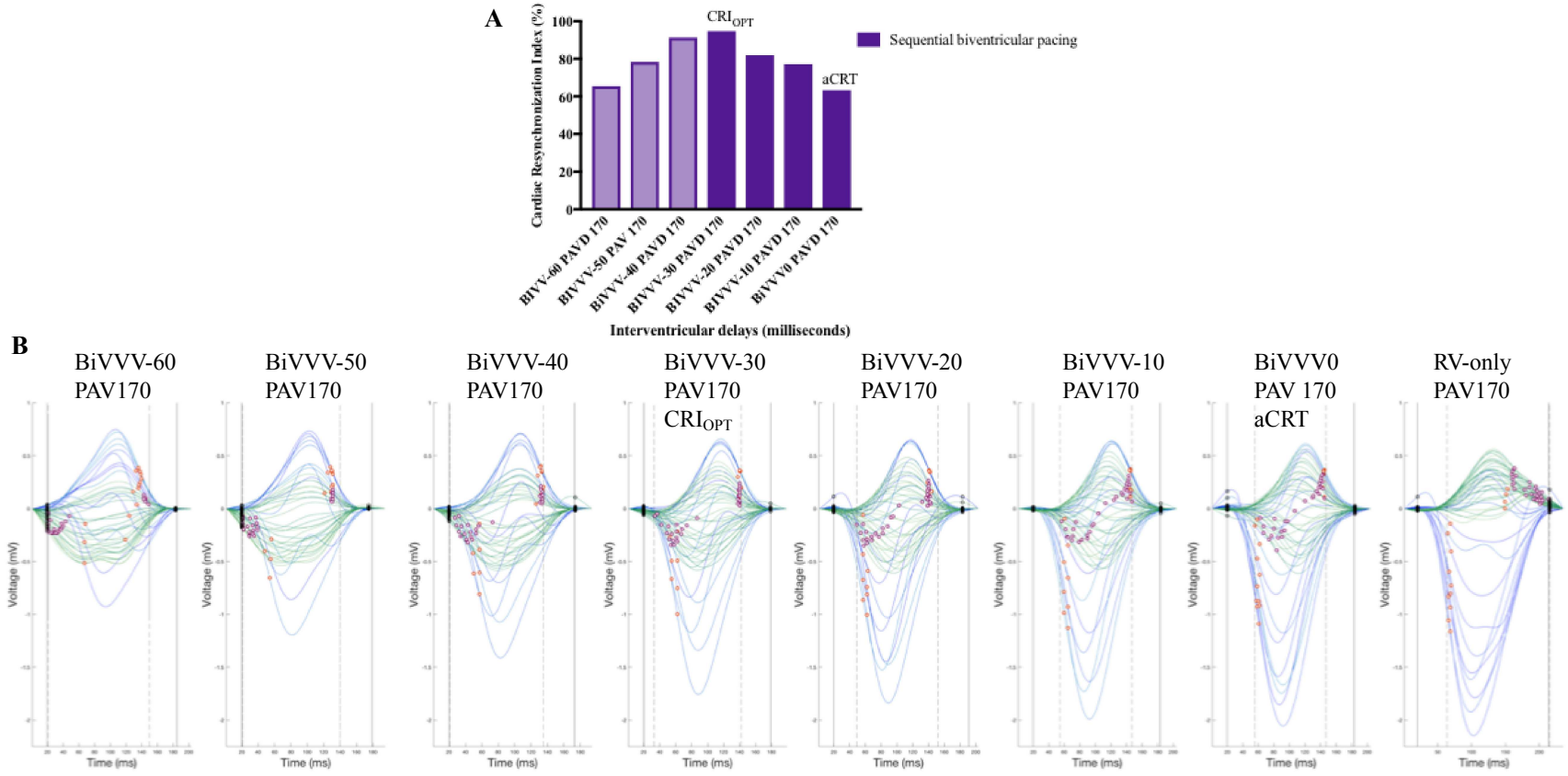
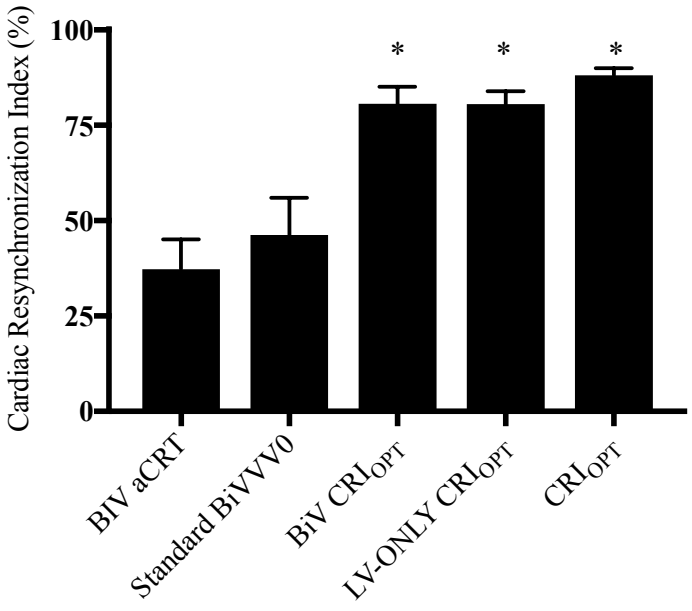


Figure 7. Electrical synchrony among patients with aCRT BiV pacing (*n*=19)



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CHAPTER 4. RELATIONSHIP BETWEEN QRS DURATION AND THERAPEUTIC WINDOW FOR CRT OPTIMIZATION

Relationship Between QRS Duration and Therapeutic Window for CRT Optimization

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SUMMARY

Aims: Cardiac resynchronization therapy (CRT) response is proportional to QRS duration (QRSd). Since conduction velocity slows in concert with QRSd widening, effective fusion of electrical wavefronts should occur more readily with wider QRSd. The objective is to examine the relationship between QRSd and the range of atrioventricular delays (AVD) that provide adequate electrical resynchronization.

Methods: A total of 122 CRT patients with left ventricular (LV) conduction delay, sinus rhythm and intact atrioventricular node conduction during LV-only pacing were included in this analysis. Patients were categorized into the following QRSd groups: narrow (<120ms; n=20); moderate (120 to 150ms, n=37); and prolonged (≥150ms; n=65). Electrical synchrony was quantified as cardiac resynchronization index (CRI) using multi-lead electrocardiographic systems and a proprietary algorithm that quantified wavefront fusion. A Gaussian distribution equation was fitted to CRI response.

Results: Peak CRI was high (87.6±6.3%) and similar (p=0.716) across QRSd groups. The standard deviation of the Gaussian distribution significantly correlated with QRSd (R=0.614, p<0.001), and also progressively and significantly (p<0.001) increased as QRSd increased from narrow (34.8±10.0ms), to moderate (50.6±8.4ms), to prolonged (67.6±18.3ms). At an AVD 40ms from optimal, CRI differed significantly (p<0.001) between groups, with progressively higher CRI values as native QRSd increased.

Conclusion: Electrical resynchronization with optimally programmed CRT during LV-only pacing was similar between patients with varying QRSd. The therapeutic window that corresponded with optimal electrical resynchronization decreased in proportion to native QRSd. This finding may provide one potential explanation regarding the previous discouraging reports on the efficacy of CRT in narrow QRSd patients.

Key words: Cardiac resynchronization therapy, Heart failure, Electrocardiography, Electrical dyssynchrony

WHAT'S NEW?

- This analysis examined the relationship between intrinsic QRS duration and atrioventricular delay optimization with changes in electrical synchrony using a novel methodology based on the concept of wavefront fusion and cancellation
- Changes in electrical synchrony during atrial-synchronized LV-only pacing in patients with either LBBB and IVCD conduction exhibited a binomial distribution, with suboptimal electrical synchrony at short and long atrioventricular delays, and a peak that occurred at an intermediate atrioventricular delay
- All patients, and independent of intrinsic QRS duration, exhibited similar improvements in the percent peak electrical resynchronization during LV-only pacing
- The width of the binomial distribution was dependent on intrinsic QRS duration, with narrower durations associated with a narrower range of atrioventricular delays that corresponded with good electrical synchrony
- These results further emphasize the importance of atrioventricular device optimization with improving electrical synchrony in patients with varying QRS durations

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a well-established treatment for patients with systolic heart failure (HF), left ventricular (LV) ejection fraction (LVEF) < 35%, and a prolonged QRS duration (QRSd) (Abraham et al., 2002). Multiple studies report QRSd to be an important predictor of response to CRT (Poole et al., 2016). Thus, guidelines recommend CRT implantation for patients with LBBB and a QRSd of at least 150 milliseconds as Class I indicated (Level of Evidence A), while CRT in patients with a narrow QRSd less than 130 milliseconds is Class III contraindicated (Level of Evidence A) (Ponikowski et al., 2016). In addition, although some single-center studies have shown benefit of CRT in narrow QRSd patients (Achilli et al., 2003; Bleeker, Holman, et al., 2006; Muto et al., 2013; Yu et al., 2006), randomized trials have failed to confirm this, including RethinQ (Beshai et al., 2007), EchoCRT (Ruschitzka et al.,

2013), and Lesser Earth (Thibault et al., 2011). Two meta-analyses have shown that CRT implantation in narrow QRSd patients is associated with a poor prognosis (Shah et al., 2015; Wang et al., 2015).

Wider QRSd patients tend to have greater electrical dyssynchrony. Since CRT is thought to exert its beneficial effect by improving electrical dyssynchrony (Sweeney et al., 2010), and subsequently mechanical dyssynchrony, it should produce LV remodeling and systolic function improvements in proportion to the severity of the underlying substrate defect. However, an additional reason for the correlation between response to CRT and QRSd could be that the therapeutic window for effective CRT programming widens in proportion to QRSd. This is a plausible hypothesis because conduction velocity decreases as QRSd increases (Bacharova et al., 2010; Zweerink et al., 2017). If CRT produces its beneficial effect by improving fusion of native, RV-paced (RVp) and LV-paced (LVp) wavefronts (Strik, van Middendorp, et al., 2013), then the slower the conduction velocity, as evidenced by a prolonged native QRSd, the more likely any given standard CRT atrioventricular (AV) delay (AVD) setting should result in adequate electrical resynchronization.

A novel method for measuring relative improvements in electrical synchrony in patients with CRT, as based on the concept of wavefront fusion and electrocardiographic cancellation, has recently been developed (Bank et al., 2020). It is hypothesized that the narrower the QRSd, the more precise the AVD programming would be needed in order to produce optimal ventricular wavefront fusion. In order to test this hypothesis, improvements in electrical synchrony with AVD optimization during atrial-synchronized LV-only pacing (representing fusion of native and LVp wavefronts) were measured in CRT patients of varying intrinsic QRSd, and the width of the therapeutic window that produced optimal electrical resynchronization was determined.

METHODS

Study population

This was a retrospective analysis of HF patients (n=122) who received a CRT pacemaker or defibrillator between 2014 and 2020. Patients were studied between 4 days and 4 years post-implant, with over half of the patients (n=70, 57.3%) studied within two months of their CRT implant. All patients had

CRT implantation for standard indications, except for narrow QRSd patients. Inclusion criteria were: LVEF ≤ 40%, New York Heart Association (NYHA) class II to ambulatory class IV HF, and on optimal medical therapy. Patients with a non-specific interventricular conduction delay (IVCD) and/or a QRSd less than 120 milliseconds, but with an ECG pattern consistent with LV conduction delay, were included in the analysis. Patients with <90% ventricular pacing, permanent atrial fibrillation, complete heart block, or right bundle branch block were excluded from the study. This study was approved by an Institutional Review Board (IRB); all patients signed and gave informed consent.

Clinical 12-lead ECGs

Standard 12-lead ECGs were acquired during native rhythm (i.e., CRT off), and the PR interval and QRSd were measured. Patients were stratified into the following QRSd groups: narrow (<120 milliseconds); moderate (≥120 and <150 milliseconds); and prolonged (≥150 milliseconds). LBBB was defined as having a QRSd greater than 120 milliseconds, slurred R waves with no Q waves in the lateral leads (e.g., I, aVL, V_5, V_6), and a negative terminal deflection (e.g., QS, rS) in lead V_1 (Caputo et al., 2018). Both IVCD and narrow QRSd patients had characteristics of delayed LV conduction (QS or rS complex in lead V_1, negative area under the curve [AUC]).

CRT Device Interrogation and ECG Data Acquisition Protocol

A device interrogation assessed percent atrial and ventricular pacing, arrhythmia burden, ventricular ectopy, lead thresholds, and the atrial-sensed RV-sensed (AsRVs) or atrial-paced RV-sensed (ApRVs) intervals. Data was acquired with one of two investigational ECG Belt systems, or a multi-lead ECG system. One of the ECG Belt systems consisted of 53 electrodes (*n*=75), with 17 anterior and 36 posterior unipolar electrodes (Verathon Inc, Bothell, WA; modified by Medtronic, Mounds View, MN) (Bank et al., 2018; Gage et al., 2017). The other ECG Belt system consisted of 40 electrodes (*n*=5), with 20 anterior and 20 posterior unipolar electrodes (Medtronic ECG Belt Research System ver. 2.0, Medtronic, Mounds View, MN). Both ECG belt systems were adhered to the patient's upper torso, and had an ECG amplifier with a storage unit. The multi-lead ECG system (*n*=42) used two different standard ECG systems

(GE Healthcare, MAC 5500 HD, Chicago, IL), which collectively consisted of a total of 18 unipolar electrodes distributed across the anterior and posterior upper torso. Electrograms were recorded during native rhythm, and at various non-experimental programming configurations during LV-only pacing over a wide range of AVDs.

Measurement of Electrical Dyssynchrony and Cardiac Resynchronization Index

All three ECG systems simultaneously recorded electrical potentials from the anterior and posterior unipolar electrodes. Electrocardiographic data was analyzed with an off-line propriety post-processing software algorithm (MATLAB, version R2018a, MathWorks, Inc., Natick, MA) (Bank et al., 2020; Curtin et al., 2018). The algorithm automatically detects QRS complexes, and calculates the difference between the areas under multiple pairs of anterior and posterior curves (AUC). Three QRS complexes were averaged during each acquired recording. Electrical synchrony was quantified by cardiac resynchronization index (CRI), and calculated as the percent improvement in AUC at any given device setting as normalized to native conduction (Bank et al., 2020).

Statistical Analysis

IBM SPSS Statistics 23 (IBM Corp. Released 2016, IBM SPSS Statistics for Mac, Version 23, Armonk, NY:IBM Crop) was used for statistical analysis. Continuous and categorical variables were presented as mean±standard deviation (SD) and counts (% of total), respectively. Electrical resynchronization during LV-only pacing was fitted to a Gaussian distribution using MATLAB software; the amplitude of the Gaussian curve represented the highest CRI, and the SD (i.e., width) of the Gaussian curve represented the therapeutic range and potential of electrical resynchronization. A one-way analysis of variance (ANOVA) with Bonferroni post-hoc comparisons assessed differences in electrical resynchronization between QRSd groups. A repeated measures ANVOA tested for within-patient differences in CRI across different AVDs.

RESULTS

Patient Population

Table 1 summarizes the baseline characteristics of the patient cohort. Average native QRSd was 144.0±26.5 milliseconds, and LVEF was 26.6±7.1%. Two-thirds of the patients had LBBB conduction (*n*=78, 63.9%). Patients were on optimal medical therapy, with 90.2% on an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB), and 98.4% on a beta-blocker. Right ventricular lead position was septal in the majority of the patients (*n*=81, 66.4%), and LV lead position was predominantly posterior/posterolateral (n=40, 32.8%) or lateral (*n*=59, 48.4%). Surgical epicardial LV leads were present in 2 patients (1.6%).

Ventricular Activation and Metrics of Electrical Synchrony during LV-Only Pacing

Figure 1 displays ventricular activation during native, or intrinsic, rhythm for a patient with a narrow QRSd using both traditional 12-lead ECGs, and also electrograms derived from the investigational 53-lead ECG belt system. The blue electrograms are the anterior electrodes, and the green electrograms are the posterior electrodes. While standard 12-lead ECG methodology displays IVCD conduction during native rhythm, the patient's native ventricular activation using the ECG belt was depicted by positively and negatively deflected posterior and anterior electrograms, respectively. This is consistent with LBBB conduction, and characterizes a leftward wave of depolarization that traverses posteriorly. The disproportionately larger amplitude of the negative anterior electrograms, as compared to the amplitude of the positively deflected posterior electrograms, corresponded with a negative AUC of -91.3 mV×milliseconds.

Electrocardiographic data was also acquired using the 53-lead ECG belt at various AVDs during LV-only pacing; specifically, between 80 to 220 milliseconds. Electrical resynchronization, as quantified by CRI, during LV-only pacing exhibited a binomial, or Gaussian, distribution with AVD optimization. In particular, at the shortest AVD of 80 milliseconds, the anterior electrodes reversed in polarity as compared to native rhythm, and were positively deflected as a result of the prevailing LVp wavefront that was paced prior to the native wavefront. The negatively deflected posterior electrodes were disproportionately smaller

in amplitude as compared to the anterior electrodes. The corresponding area encompassed under the positively deflected anterior electrodes was, thus, greater in magnitude then that of the area under the negative posterior electrodes, and was quantified by a positive AUC value of 103.1 mV×milliseconds. Positive AUC values characterize ventricular activation that is composed of a dominant anteriorly-moving LVp wavefront with minimal fusion from the native wavefront, and is represented in the bar graph as a lighter shaded bar.

The LVp wavefront occurred increasingly delayed after sensing an intrinsic, or paced, atrial contraction with progressive lengthening of the AVD, allowing for improvements in the timing between fusion of the posteriorly-moving native wavefront with the anteriorly-moving LVp wavefront. Such improvements in ventricular fusion were manifested by reduced amplitude, and also reversed polarity, of the anterior and posterior electrodes as compared to native conduction with subsequent prolongations in the AVD. The optimal AVD during LV-only pacing for the patient depicted in Figure 1 occurred at 140 milliseconds, and was quantified by the smallest AUC of -9.0 mV×milliseconds. At this pacing setting, electrical synchrony was improved due to optimal fusion between the LVp and native wavefronts, and was associated with a CRI of 90.1%. Subsequent increases in AVD resulted in increasingly negative AUC values, attributable to a greater contribution of the posteriorly-moving native wavefront to ventricular fusion. A theoretical representation of the estimated ventricular fusion between the native and LVp wavefronts is also provided at each AVD in Figure 1.

All patients included in this analysis, including narrow QRSd patients, had a native ventricular activation similar to that as shown in Figure 1, with positive posterior and negative anterior electrograms. In all patients, CRI changed incrementally with prolonging the AVD comparable to that as depicted in Figure 1, such that the relationship exhibited a binomial, or Gaussian, distribution. The average AUC during native rhythm among the patient cohort was -104.4±55.1 mV×milliseconds (Table 2). The estimated peak CRI in the total patient cohort was 87.6±6.3%, and the average SD of the Gaussian curves was 57.1±19.2 milliseconds (Table 2).

Gaussian Distribution of Electrical Resynchronization and QRSd

Figure 2 shows a strong and significant (R=0.614, p<0.001) correlation between native QRSd and SD of each patient's Gaussian curve. Table 2 displays the patients stratified into three different groups as defined by native QRSd: narrow (n=20), moderate (n=37), and prolonged (n=65). AUC differed significantly (p<0.001) among the 3 groups and increased in proportion to QRSd (narrow QRSd vs. moderate QRSd vs. prolonged QRSd: -47.0±20.4 mV×milliseconds vs. -97.3±41.7 mV×milliseconds vs. -126.4±55.6 mV×milliseconds). No differences in peak CRI were present across the QRSd groups (p=0.716). Conversely, significant group differences (p<0.001) were present in the SD of the Gaussian curves (34.8±10.0 milliseconds vs. 50.6±8.4 milliseconds vs. 67.6±18.3 milliseconds), with SD increasing concurrently as QRSd increased.

Figure 3 displays individual and group average Gaussian curves. Figure 4 shows the group average distributions in electrical resynchronization, which emphasize the similarity in peak CRI, as well as the difference in SD (i.e., curve width) between the QRSd groups. The vertical dashed lines with circles depict the CRI for each QRSd group at the optimal AVD, and also at AVDs that were 20, 40 and 60 milliseconds longer then the optimal AVD. As shown in Figure 4 and in Table 3, CRI at any given non-optimal AVD was significantly greater the wider the QRSd. Results from a repeated measures ANOVA report significant within-group differences in CRI with increasing AVDs (p<0.001, all QRSd groups). When comparing differences in CRI between QRSd groups, patients with a narrow QRSd had significantly lower CRI (58.8±15.1%) at an AVD that was only 20 milliseconds longer than the optimum as compared both moderate (74.8±6.9%, p<0.001) and prolonged QRSd (78.7±6.1%, p<0.001) (Table 3). When the AVD was 40 milliseconds longer than the optimum AVD, moderate QRSd patients had a significantly lower CRI (46.3±11.8%) as compared to prolonged QRSd patients (58.2±11.5%, p<0.001).

Figure 5 demonstrated the impact of intrinsic QRSd on response to CRT. In 5A, the average fitted Gaussian curves for the three QRSd groups are displayed. Three hypothetical relationships, as shown in 5B, display the effect QRSd exerts on the relationship between electrical resynchronization during CRT pacing with subsequent improvements in LVEF. It is generally accepted that greater electrical dyssynchrony occurs with prolonged QRSd, which should correspond to greater potential for improvement in LVEF.

Thus, prolonged, moderate, and narrow QRSd patients are depicted with a maximum LVEF improvement of 30%, 20% and 10%, respectively. Using the data from Table 4, the estimated LVEF improvement with CRT, as based on QRSd and on percent electrical resynchronization, is demonstrated. As shown, if a patient with wide QRSd is programmed 40 milliseconds from optimal, the correspond CRI is 58.1% and LVEF improvement is 17.5%. In contrast, if a patient with narrow QRSd is programmed 40 milliseconds from optimal, the CRI is 20.7% and LVEF improvement is 2.5%.

DISCUSSION

In this study, LV-only pacing at the optimal AVD resulted in approximately 88% electrical resynchronization. All patients exhibited a binomial distribution of CRI response with AVD optimization. Large and similar improvements in peak electrical resynchronization occurred independent of native QRSd during LV-only pacing. QRS duration strongly correlated with the width of the binomial distribution, describing the relationship between AVD optimization and potential for electrical resynchronization. The longer the QRSd, the greater the range of AVDs that could achieve adequate electrical resynchronization. Therefore, the likelihood that any non-optimal AVD during LV-only pacing will result in adequate electrical resynchronization increases in proportion to QRSd. This finding provides one reason why QRSd predicts response to CRT and may, in part, explain why patients with narrow QRS have previously not been shown to benefit from CRT in randomized clinical trials.

QRSd and response to CRT

QRS duration has been used as one of the main enrollment criteria for all large multicenter studies of CRT, and is a key component of all CRT guidelines (Ponikowski et al., 2016). In addition, multiple CRT studies have shown that clinical and/or echocardiographic response to CRT increases as QRSd lengthens (Birnie, Ha, et al., 2013; Gold et al., 2012; Kang et al., 2015; Peterson et al., 2013). This observation is not surprising since QRSd is a marker of electrical, and mechanical, dyssynchrony (Haghjoo et al., 2007). Since the premise of CRT is to correct underlying electrical dyssynchrony, the more abnormal the electrical

substrate, the greater the expected improvement. In this paper, data supporting an additional explanation for the positive relationship between QRSd and CRT response is provided. Specifically, the greater therapeutic window for AVD programming results from a wider QRSd.

Improvements in electrical resynchronization during AVD optimization with LV-only pacing in patients with left ventricular conduction delay, including LBBB and IVCD conduction, were measured in this retrospective analysis. In all the 122 patients studied, the relationship between AVD and CRI exhibited a binomial distribution. Although the relationship between CRI and AVD were similar in all patients regardless of QRSd, the width of the binomial distribution increased in proportion to QRSd. This finding is in agreement with past reports demonstrating an inverse relationship between conduction velocity and QRSd (Quintanilla et al., 2017). Since patients with wide QRSd have the slowest conduction velocities, an AVD that varies from optimal has a better chance of resulting in fusion of native and LVp wavefronts as compared to patients with narrower QRSd. Thus, if patients are programmed at a standard AVD without the benefit of a technology that effectively optimizes electrical resynchronization, any variance from the optimal AVD will result in a negative effect on resynchronization that is magnified in proportion to the narrowness of the QRSd.

CRT Optimization

Numerous methods of optimizing CRT programming have been studied. Some are performed at a single point in time in clinic and include either echocardiography (Barold et al., 2008), or standard ECGs (Cooper et al., 2014; Gage et al., 2018; Sweeney et al., 2014). Other methods utilize pacing algorithms built into CRT devices that alter programming automatically (Abraham et al., 2010; Ellenbogen et al., 2010; Kamdar et al., 2010; Martin et al., 2012). Despite extensive research on CRT optimization, no methodology has been generally accepted and routinely used in clinical practice. In fact, 80-90% of patients are left at their initial, or nominal, CRT settings (Gras et al., 2009). In a previous study, we used a simple qualitative assessment of wavefront fusion from 12-lead ECGs to optimize CRT patients, and showed significant improvements in LVEF as compared to standard non-optimized settings (Gage et al., 2018). A new quantitative methodology for CRT optimization that is based on the concept of wavefront fusion and

electrocardiographic cancellation has been since developed (Bank et al., 2020). Previous research using this methodology demonstrated that the optimal timing of native, RVp, and LVp wavefronts can be determined during biventricular pacing at different AVDs or interventricular delays, and also with LV-only pacing (Bank et al., 2020). LV-only pacing, and not biventricular pacing, was evaluated in this retrospective analysis since it is more straightforward, owning to fusion of only the native and LVp wavefronts. Analysis and interpretation of biventricular pacing is complicated since the contribution of native and RVp wavefronts to ventricular fusion varies; ventricular fusion is heavily weighted towards the RVp wavefront contribution at short AVDs, while the native wavefront is more dominant at longer AVDs (Vernooy, Verbeek, et al., 2007).

In the large multicenter studies of CRT, either CRT optimization was not performed, it was done non-uniformly, or it was performed using a wide variety of different methodologies. Therefore, most of the data from these trials reflects the effects of CRT on patients programmed to standard, not individually-optimized, device settings. The findings in this study are relevant since it demonstrates the importance that CRT optimization is inversely proportional to QRSd. Patients with a prolonged QRSd (>150 milliseconds) have a greater therapeutic window and, thus, a standard setting is more likely to result in a higher relative improvement in electrical resynchronization as compared to patients with narrower QRSd.

Narrow QRS

Single-center studies have shown some potential benefit of CRT in patients with narrow QRS. Multi-center randomized studies of narrow QRSd patients, including RethinQ, Echo-CRT, Lesser Earth, have mostly been negative (Beshai et al., 2007; Ruschitzka et al., 2013; Thibault et al., 2011); although, NARROW-CRT showed some evidence of improved clinical outcomes in ischemic patients (Muto et al., 2013). Two meta-analyses have shown that CRT implantation among narrow QRSd patients is associated with poor outcomes (Shah et al., 2015; Wang et al., 2015). The 20 patients with narrow QRS in this study did not have normal conduction. Mean QRSd was 103.5±10.9 ms, AUC was -47.0±20.4 mV×milliseconds, and 12-lead ECG showed evidence of delayed LV activation, with either incomplete LBBB or IVCD conduction. All patients had electrogram morphologies similar to that shown in Figure 1, with a relatively

uniform posteriorly-moving wavefront suggestive of delayed LV activation that is characteristic of LBBB conduction. These patients appear to have an electrical abnormality that was similar to, although less severe, than the wider QRSd patients. Supporting this concept was the finding that narrower QRSd exhibited improvements in electrical synchrony similar in magnitude to prolonged QRSd patients, and also exhibit similar dose-response changes in CRI with increasing AVDs. As shown in Figure 5, one reason it might be difficult to demonstrate an echocardiographic response in narrow QRSd patients is that they have less electrical dyssynchrony, which translates into less potential for subsequent echocardiographic response. An additional reason, demonstrated in this study, is that the therapeutic window for CRT optimization is very narrow in these patients. For example, even if the AVD during LV-only pacing is only 20 milliseconds off from optimal, CRI decreases from 86.1% at optimal AVD to 56.5%.

Limitations

This analysis investigated the effect of AVD optimization with corresponding improvements in electrical synchrony during LV-only pacing, but did not evaluate device optimization of the AVDs and interventricular delays during biventricular pacing. If our concept of wavefront fusion is correct, changes in electrical synchrony with interventricular delay optimization at short AVDs, during which ventricular activation is primarily characterized of fusion between RVp and LVp wavefronts and with minimal contribution from the native, should exhibit a similar binomial distribution. Patients with atrial fibrillation may also exhibit a binomial distribution in electrical resynchronization with interventricular delay optimization, owning to the lack of native conduction to fuse with the paced ventricular wavefronts. The linear relationships between percent electrical resynchronization and improvement in LVEF were assumed. Although the relationship may not be linear, improvements in LVEF and native QRSd are likely strongly and positively correlated, and the concepts shown should be valid regardless of the exact shape of the dose-response relationship. Lastly, this was also a retrospective analysis and patients did not have CRT programming optimized according to CRI, which precludes establishing a causal relationship between CRI with subsequent echocardiographic response.

CONCLUSION

Using a new methodology that measures wavefront fusion and electrocardiographic cancellation, dose-dependent changes in electrical synchrony with AVD optimization that resemble a Gaussian distribution were observed during LV-only pacing in patients with varying QRSd. At the optimal AVD, peak CRI is approximately 88% and is not significantly different between QRSd groups. However, the range of AVDs that correspond to adequate electrical resynchronization increases in proportion to QRSd. It is concluded that QRSd predicts CRT response in non-optimized patients in part because of a wider therapeutic window for programming AVDs. This study also shows that CRT optimization in narrower QRSd patients can improve electrical synchrony, and raises the possibility that CRT optimization could result in beneficial response in patients that were previously thought to derive no benefit from CRT.

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ABBREVIATIONS

ACEI = Angiotensin-converting enzyme inhibitor

ApRVs = Atrial-paced RV sensed interval

ARB = Angiotensin-receptor block

AsRVs = Atrial-sensed RV sensed interval

AUC = Area under the curves

AV = Atrioventricular

AVD = Atrioventricular delay

CRI = Cardiac resynchronization index

CRT = Cardiac resynchronization therapy

ECG = Electrocardiogram

HF = Heart failure

IRB = Institutional Review Board

IVCD = Interventricular conduction delay

LBBB = Left bundle branch block

LV = Left ventricular

LVp = Left ventricular paced

LVEF = Left ventricular ejection fraction

NYHA = New York Heart Association

QRSd = QRS duration

RV = Right ventricular

TABLE LEGENDS

Table 1. Baseline demographics and clinical characteristics.

Table 2. Electrical resynchronization metrics stratified by QRSd.

Table 3. Electrical resynchronization variance from optimal stratified by QRSd

TABLES

Table 1. Baseline demographics and clinical characteristics

	Total (*n*=122)
Male, n (%)	80 (65.2)
Age (years)	67.4±11.3
Body mass (kg)	91.2±19.1
Height (cm)	172.1±10.9
Body mass index (kg/m^2)	30.8±6.0
Ejection fraction (%)	26.6±7.1
LV end systolic volume (mL)	125.9±52.4
LV end diastolic volume (mL)	168.6±59.3
NYHA class, n (%)	
II	43 (35.2)
III	77 (63.1)
IV	2 (1.9)
Ischemic cardiomyopathy, n (%)	53 (43.4)
Native QRSd (ms)	144.0±26.5
Native PR interval (ms)	194.5±37.8
1st degree AV block, n (%)	53 (43.4)
QRS morphology, n (%)	
LBBB	78 (63.9)
IVCD	44 (36.1)
RV lead, n (%)	
Apical	24 (19.7)
Septal	81 (66.4)
Unknown	17 (13.9)
LV lead position, n (%)	
Anterior/anterolateral	6 (4.9)
Lateral vein	59 (48.4)
Posterior/posterolateral	40 (32.8)
Epicardial	2 (1.6)
Unknown	13 (10.7)
ACEI/ARB, n (%)	110 (90.2)
Beta blockers, n (%)	120 (98.4)
Digoxin, n (%)	11 (9.0)
SARA, n (%)	35 (28.7)

Continuous and categorical variables presented as mean±standard deviation (SD) and counts (% of total), respectively.

Abbreviations: ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; AV, Atrioventricular; IVCD, Interventricular conduction delay; LBBB, Left bundle branch block; LV, Left Ventricular; NYHA, New York Heart Association; QRSd, QRS duration; RV, Right Ventricle; SARA, Selective aldosterone receptor antagonist.

Table 2. Electrical resynchronization metrics stratified by QRSd.

	Total	**Narrow (< 120 milliseconds)**	**Moderate (120-150 milliseconds)**	**Prolonged (>150 milliseconds)**	***p*-value**
n	122	20	37	65	
Native QRSd (milliseconds)	144.0±26.5	103.5±10.9†‡	130.5±8.1‡	164.2±14.9	<0.001
Peak CRI (%)	87.6±6.3	87.2±7.8	88.3±6.0	87.3±6.0	0.716
Gaussian curve σ (milliseconds)	57.1±19.2	34.8±10.0†‡	50.6±8.4‡	67.6±18.3	<0.001
Native AUC (m×*milliseconds)	-104.4±55.1	-47.0±20.4†‡	-97.3±41.7‡	-126.4±55.6	<0.001

Mean±SD.

Abbreviations: AUC, area under the curve; CRI, cardiac Resynchronization Index; QRSd, QRS duration.

p-values are from a one-way ANOVA.

† significantly different than moderate QRSd patients ($p<0.05$).

‡ significantly different than prolonged QRSd patients ($p<0.05$).

Table 3. Electrical resynchronization variance from optimal stratified by QRSd

	Total	**Narrow (< 120 milliseconds)**	**Moderate (120-150 milliseconds)**	**Prolonged (>150 milliseconds)**	***p*-value**
CRI at optimal AVD (%)	87.6±6.3	87.2±7.8	88.3±6.0	87.3±6.0	0.716
CRI at 20 milliseconds from optimal AVD (%)	74.3±10.9	58.8±15.1†‡	74.8±6.9	78.7±6.1	<0.001
CRI at 40 milliseconds from optimal AVD (%)	48.8±17.5	23.2±15.6†‡	46.3±11.8‡	58.2±11.5	<0.001
CRI at 60 milliseconds from optimal AVD (%)	27.7±17.3	6.9±8.1†‡	22.5±13.0‡	37.1±14.5	<0.001

Abbreviations: AVD, Atrioventricular delay, CRI, Cardiac resynchronization index; QRSd, QRS duration.
p-values are from a one-way ANOVA.
† significantly different than moderate QRSd patients ($p<0.05$).
‡ significantly different than prolonged QRSd patients ($p<0.05$).

FIGURE LEGENDS

Figure 1. Binomial distribution of improvements in electrical resynchronization during LV-only pacing with increasing atrioventricular delays

Intrinsic 12-lead ECGs, and ventricular activation using ECG belt technology with AVD optimization during atrial-synchronized LV-only pacing for a 52-year-old male HF patient in sinus rhythm with IVCD conduction. CRI values are represented in the bar graph; red colors are lightly shaded when the LVp wavefront is ahead of the native wavefront. Theoretical representations of wavefront fusion between native conduction and the LVp wavefront are presented below the electrocardiograms.

Figure 2. Correlations between native QRSd and standard deviation of the Gaussian distribution

R = Pearson's product correlation coefficient.

Figure 3. Gaussian distributions in electrical resynchronization during LV-only pacing, stratified by QRSd and fitted to an optimal AVD (i.e., μ) of 0 milliseconds

Individual patient-specific Gaussian distributions of CRI response during AVD optimization for narrow QRSd (*n*=20; <120 milliseconds), moderate QRSd (*n*=37; ≥120 ms and <150 milliseconds), and prolonged QRSd patients (*n*=65; ≥150 milliseconds). The dashed line represents QRSd group average Gaussian distribution.

Figure 4. Average resynchronization response during LV-only pacing, stratified by QRSd and fitted to an optimal AVD (i.e., μ) of 0 milliseconds

Gaussian distributions for narrow QRSd, moderate QRSd, and prolonged QRSd groups are presented in black, red, and blue colors, respectively. Mean with standard error represent CRI values at the optimal AVD, and also at AVDs 20 milliseconds, 40 milliseconds, and 60 milliseconds beyond the optimum AVD.

Figure 5. Theoretical impact of electrical resynchronization on improvements in LV systolic function, as stratified by QRSd group

Group average CRI response to changes in AVD are shown in A. In B, a hypothetical linear improvement in LVEF in response to CRI is shown; LVEF improvement is proportional to native QRSd, in which prolonged QRSd patients expected to have greater improvement in LVEF for any given CRI. Colored circles represent the estimated improvement in LVEF for a given variance from optimal AVD in each group.

FIGURES

Figure 1. Binomial distribution of improvements in electrical resynchronization during LV-only pacing with increasing atrioventricular delays

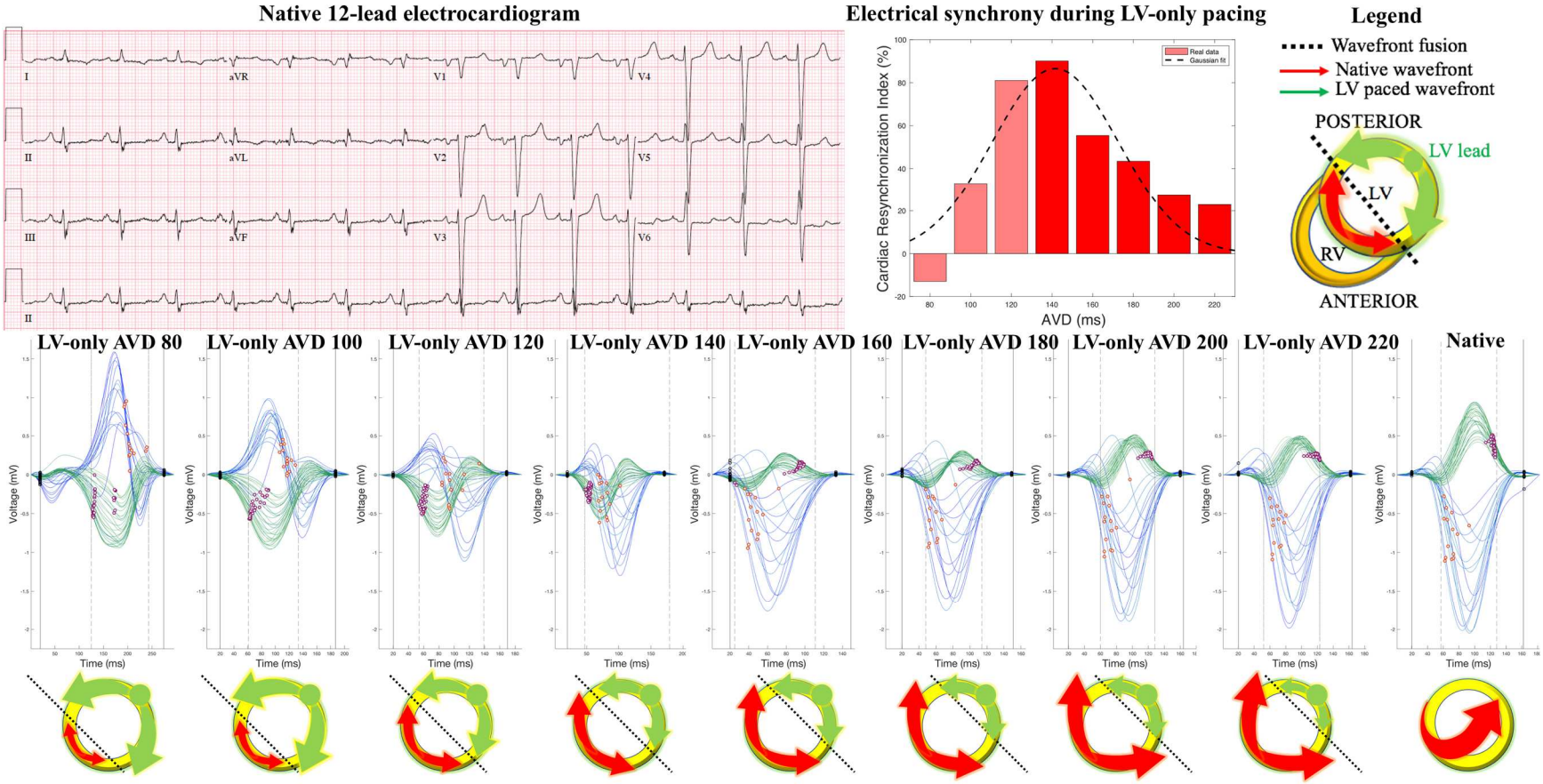


Figure 2. Correlations between native QRSd and standard deviation of the Gaussian distribution.

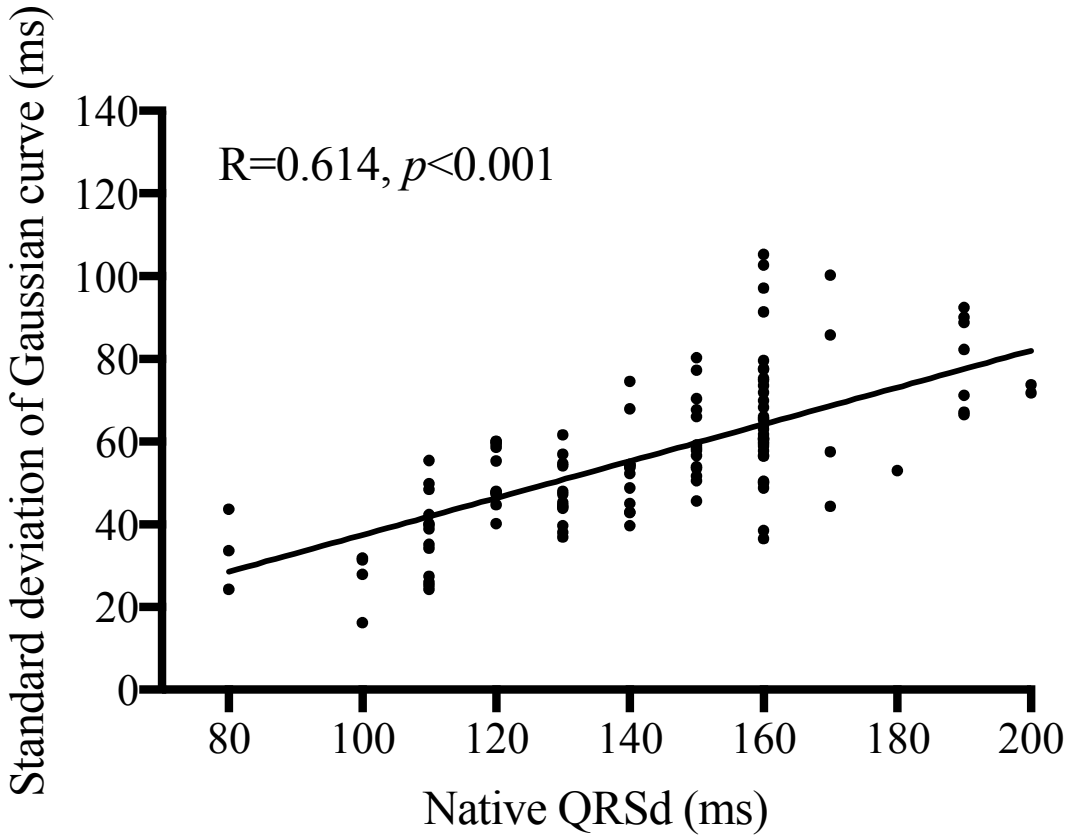
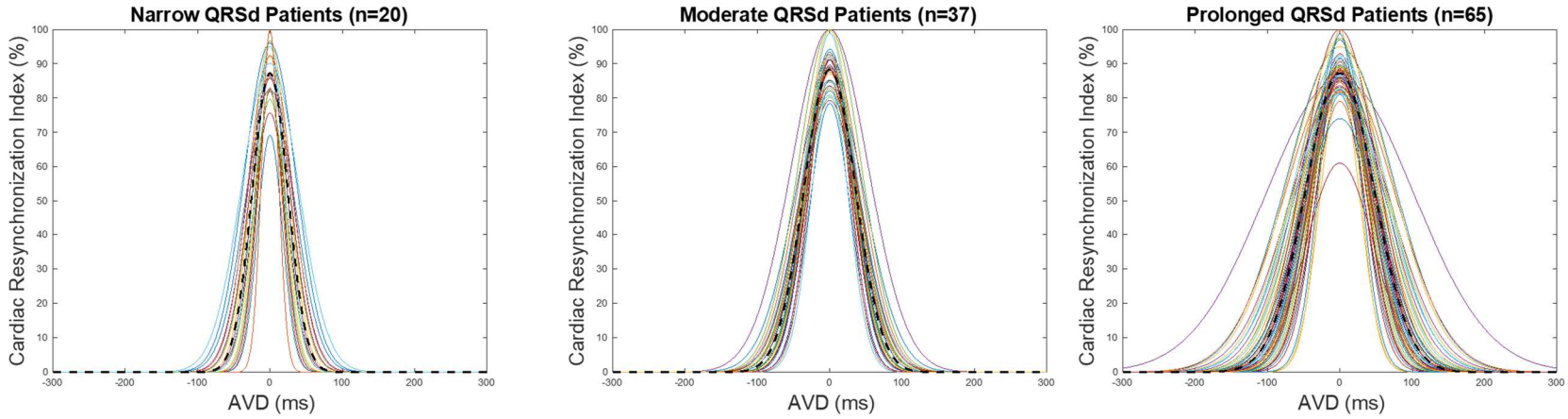


Figure 3. Gaussian distributions in electrical resynchronization during LV-only pacing, stratified by QRSd and fitted to an optimal AVD (i.e., μ) of 0 milliseconds



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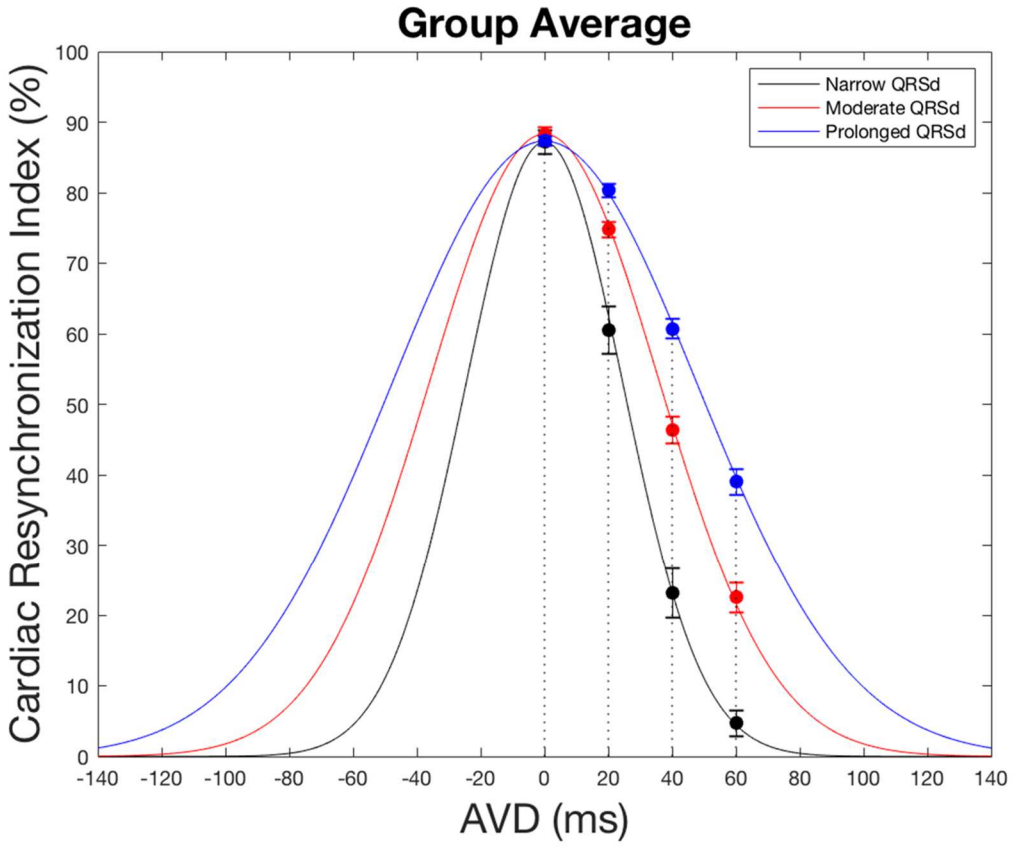

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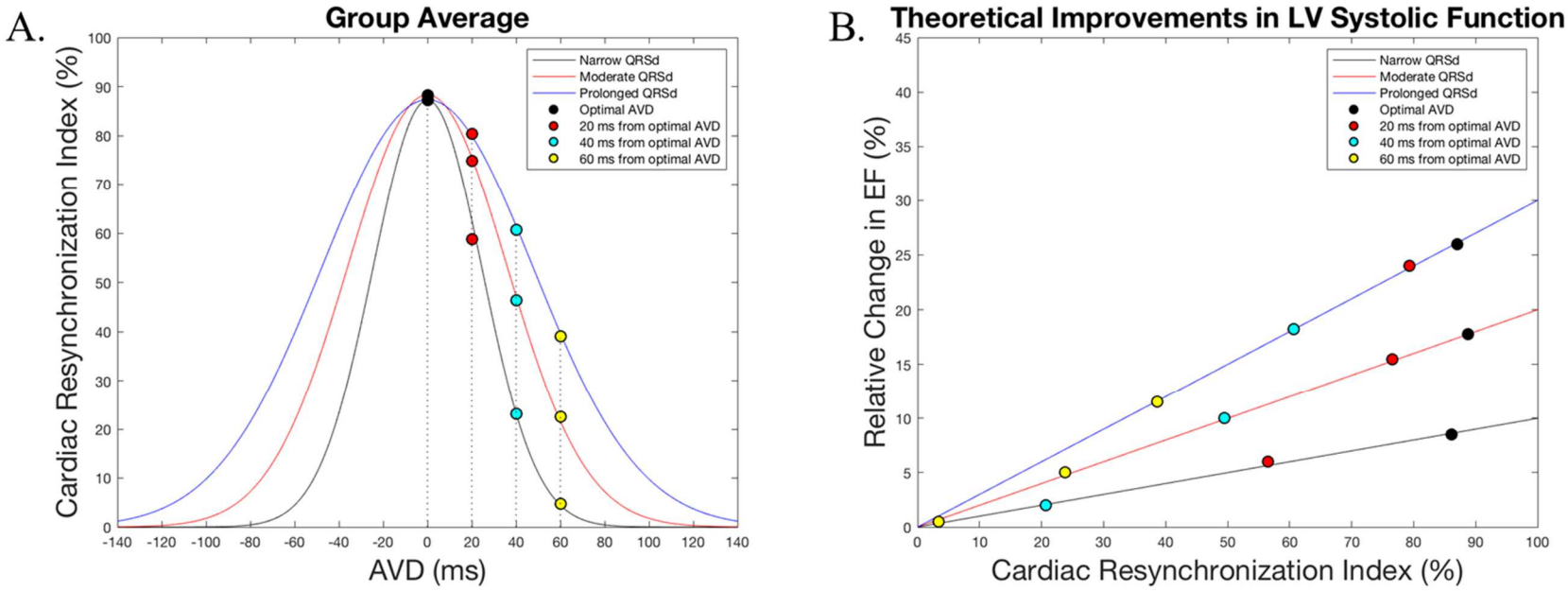

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CHAPTER 5. CONCLUSION

RESEARCH RESULTS AND IMPLICATIONS

Innovation and advancements with CRT pacemakers and defibrillators have been a tremendous breakthrough with regard to ameliorating symptoms, improving LV reverse remodeling, and reducing morbidity and mortality rates in symptomatic HF patients with electrical dyssynchrony. Current CRT devices can be programmed at various interventricular and atrioventricular delays, and quadripolar leads allow for optimizing the LV pacing vector. However, a standardized, patient-specific, and non-invasive methodology for optimizing pacing settings in an outpatient clinical setting has yet to be established. The lack of routine device optimization in standard of clinical care may cause suboptimal pacing and persistent dyssynchronous ventricular activation that is detrimental to cardiac function in a significant proportion of patients. This can potentially lead to non-response, and adverse clinical and echocardiographic outcomes.

Electrocardiographic optimization, based on evidence of wavefront fusion and cancellation on a standard 12-lead ECG, has previously been shown to correlate with improved echocardiographic response. However, the reproducibility of metrics derived from electrocardiography have been scrutinized, with reports suggesting that measures of QRSd exhibit high interobserver variability. Furthermore, assessing improvements in ventricular fusion and electrical synchrony across different pacing settings and configurations are usually not evident during a routine clinical device interrogation. Optimizing CRT devices as based on electrocardiographic characteristics of wavefront fusion is cumbersome and, thus, is very seldomly performed in standard of care clinical medicine.

This dissertation provides further evaluation on the utility of electrocardiography, in particular, the novel application of placing electrodes on the anterior and posterior upper torso in measuring myocardial electrical wavefront fusion and cancellation during CRT pacing. Two different investigational systems, namely the ECG belt and the multi-lead ECG system, were used in this dissertation. The first purpose of this dissertation was to use the ECG belt to quantify how an adaptive device-based algorithm that optimizes pacing configurations, as well as the interventricular and atrioventricular delays, improves myocardial electrical synchrony. While past reports on the superiority of LV-only pacing as compared to biventricular pacing have been conflicted, we report that electrical synchrony was improved by over 70% in patients programmed to the LV-only pacing, as compared to a 37% improvement in electrical synchrony in patients

programmed to biventricular pacing. In roughly half of the patients that were optimized to LV-only aCRT pacing, the atrioventricular delay selected by the algorithm differed by less than 10 milliseconds as compared to the atrioventricular delay that coincided with the highest percent electrical resynchronization. In patients programmed to the biventricular component of the pacing algorithm, significant improvements in electrical resynchronization were observed by optimizing the interventricular delay with LV preactivation, or also by changing pacing configurations to LV-only pacing. The importance of this finding is that optimal electrical synchrony commonly occurs during sequential biventricular pacing as compared to simultaneous pacing. Another important finding is that LV-only pacing improves electrical synchrony to a greater degree than standard biventricular pacing in the subset of patients with intact atrioventricular conduction.

The potential, referred to as the therapeutic window, for electrical resynchronization during LV-only pacing in patients with IVCD and LBBB conduction was also evaluated in this dissertation. It was discovered that LV-only pacing exhibited a binomial, or Gaussian, distribution in electrical resynchronization with atrioventricular delay optimization. Suboptimal electrical synchrony occurred at short and prolonged atrioventricular delays, while optimal electrical synchrony occurred at an intermediate atrioventricular delay. Short atrioventricular delays corresponded with suboptimal electrical resynchronization due to a greater contribution of the LV paced wavefront to ventricular activation. After reaching optimal electrical resynchronization at an intermediate atrioventricular delay, further prolongation of the atrioventricular delay resulted with decrements in electrical synchrony due to a greater contribution of the dyssynchronous native wavefront, and minimal fusion with the anteriorly-moving LV paced wavefront. The peak electrical resynchronization at the optimal atrioventricular delay was not significantly different between patients with varying QRSd. Importantly, as compared to patients that had either a moderate (≥120 milliseconds and <150 milliseconds) or prolonged QRSd (≥150 milliseconds), the standard deviation of the binomial distribution was significantly smaller in patients with a narrow QRSd (<120 milliseconds). This is reflective of a considerable narrower range of atrioventricular delays that correspond with significant improvements in electrical resynchronization. This finding emphasizes the importance of atrioventricular delay optimization during LV-only pacing. It also highlights the possibility that

atrioventricular optimization could result in beneficial response in patients with narrow QRSd, of which are a subset of patients that were previously thought to derive no benefit from CRT.

This dissertation used a novel methodology that measured myocardial electrical resynchronization via the simultaneous acquisition of ventricular activation from the upper anterior and posterior torso. The results from this dissertation quantified relative improvements in electrical synchrony during CRT pacing from an ambulatory device-based pacing algorithm. This dissertation also emphasized the importance of atrioventricular delay optimization during LV-only pacing in IVCD and LBBB patients with varying QRSd. The technology described in this dissertation provides a patient-specific and individualized assessment of wavefront fusion and cancellation during CRT pacing. It has the widespread applicability to be implemented in device optimization clinics as standard of care for CRT patients with the hopes of decreasing non-response, and improving echocardiographic and clinical outcomes.

FUTURE RESEARCH

Further research is needed to evaluate the effect of native QRS morphology on the corresponding potential for electrical resynchronization during simultaneous and sequential biventricular pacing. The comparison of native electrical dyssynchrony with metrics derived from this technology across different definitions of LBBB conduction remains to be published. Superiority of device optimization guided by CRI, as compared to standard simultaneous biventricular at an empiric atrioventricular delay, with improving echocardiographic and clinical outcomes also remains to be established. Prospective randomized studies are needed to quantify clinical and echocardiographic response rates as a result of CRT optimization with this methodology. While metrics derived from both the ECG belt and multi-lead ECG system exhibit high intra-day reproducibility, the inter-day reproducibility is unknown. Research is needed to longitudinally measure within-patient changes of native electrical dyssynchrony and percent electrical resynchronization during CRT pacing. Implementing this technology to assess the effect of patient-specific alterations in medications that affect the ionotropic (e.g., digoxin) and chronotropic (e.g., beta-blockers) properties of the myocardium with corresponding changes in native electrical dyssynchrony, and also the potential for electrical resynchronization, has yet to be conducted.

CHAPTER 6. REFERENCES

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CHAPTER 7. APPENDIX

CASE REPORT ON THE QUALITATIVE ASSESSMENT OF WAVEFRONT FUSION AND CANCELLATION USING THE INVESTIGATIONAL ECG BELT SYSTEM

Traditional 12-lead ECGs

Figure 1 displays 12-lead ECGs from a 72 year old male in sinus rhythm and with intrinsic LBBB conduction prior to CRT implant. Mid-QRS notching, in conjunction with the absence of Q waves, was observed in the lateral leads (e.g., I, aVL, V_5, V_6). Dominant negative deflections were also depicted in the anterior precordial leads (e.g., V_1, V_2), further confirming a LBBB diagnosis. The programmed CRT setting was standard simultaneous biventricular pacing at an atrioventricular delay of 100 milliseconds. Despite a lack of QRSd narrowing, improved electrical synchrony was apparent by the emergence of an R wave in the anterior precordial lead V_1, R wave regression in the augmented limb lead aVL, and a frontal axis deviation shift.

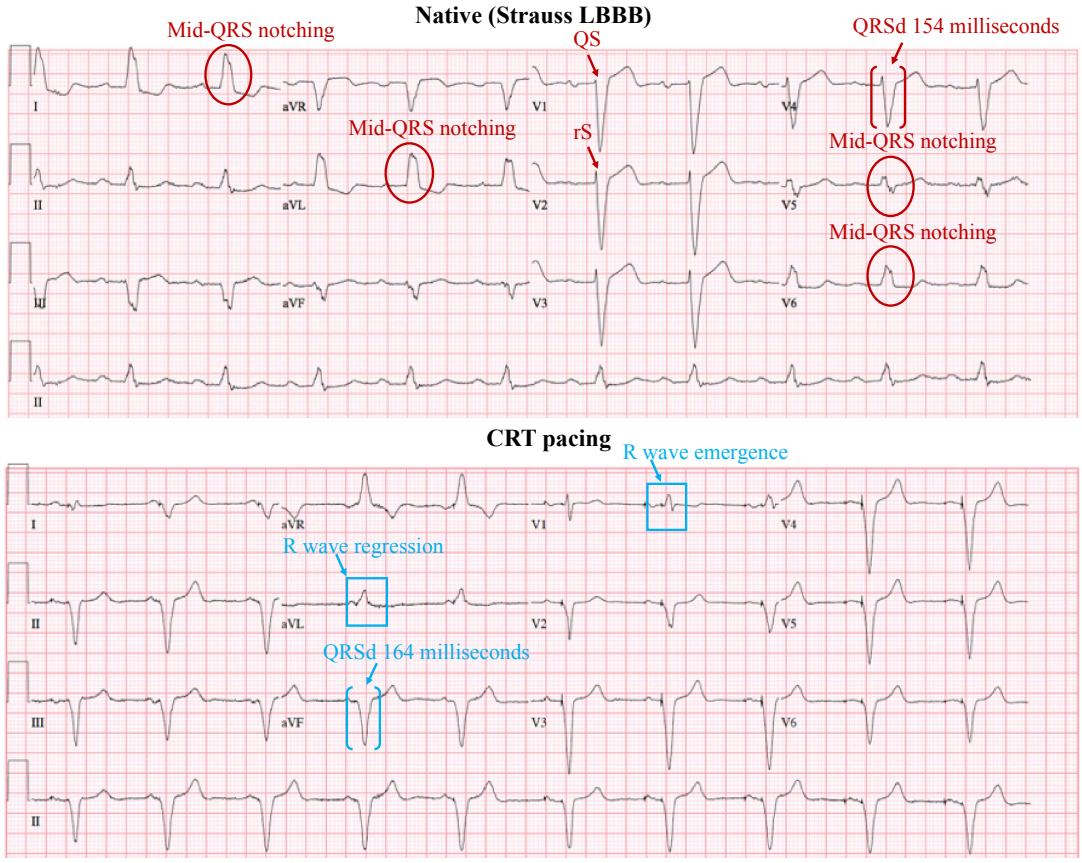

Figure 1. *Standard 12-lead ECGs of native (Strauss LBBB) conduction, and CRT pacing of standard simultaneous biventricular pacing at a sensed atrioventricular delay of 100 milliseconds*

Abbreviations: CRT, Cardiac resynchronization; LBBB, Left bundle branch block; QRSd, QRS duration

Investigational ECG belt system

By using the investigational 53-lead ECG belt (Verathon Inc, Bothell, WA, and modified by Medtronic plc, Mounds View, MN), wavefront fusion and cancellation during CRT pacing was further characterized for this patient by morphological changes in amplitude of the anterior (blue) and posterior (green) electrocardiograms, and also by narrowing of the ventricular fusion complex. Characteristic to

LBBB conduction is a unidirectional wave of depolarization that traverses posteriorly, demonstrated by positive and negative deflections in the posterior and anterior electrocardiograms, respectively (Figure 2). Improved electrical synchrony during standard simultaneous biventricular pacing was apparent via reduced amplitudes of the anterior and posterior electrocardiograms.

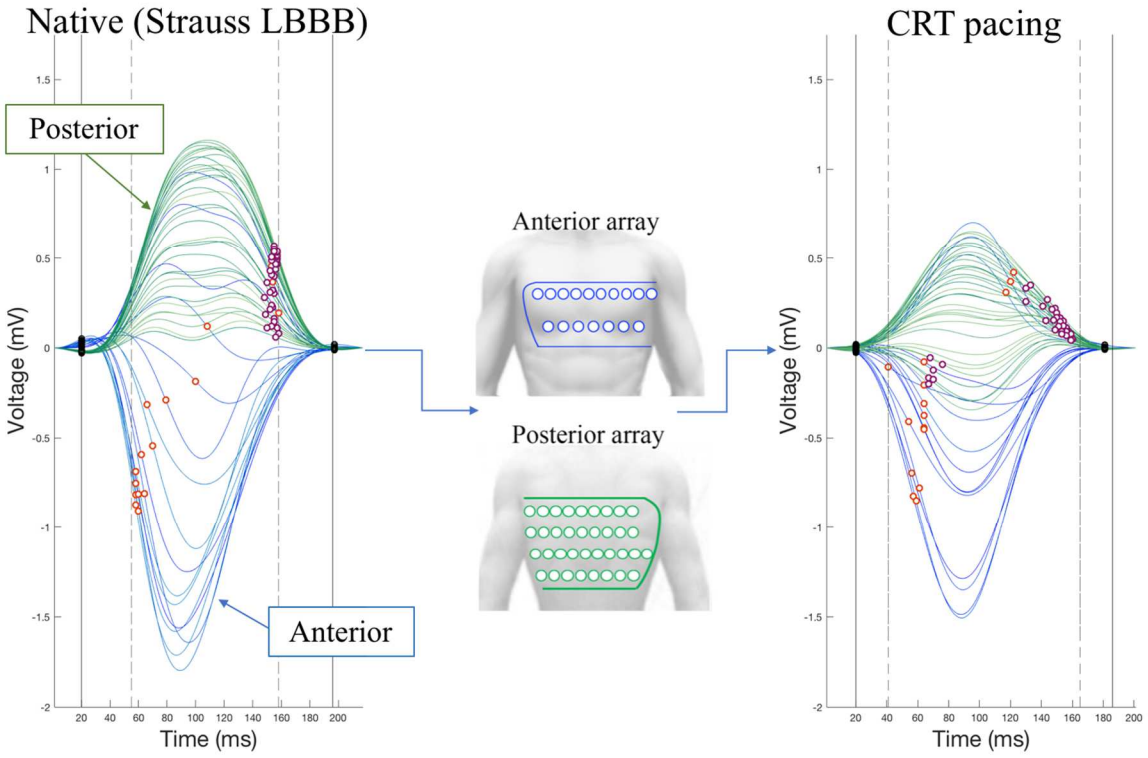

Figure 2. *Electrode placement for the 53-lead ECG belt, and body surface multichannel electrocardiograms during native (Strauss LBBB) conduction and with standard simultaneous biventricular pacing at a sensed atrioventricular delay of 100 milliseconds*

Signals recorded from the 17 anterior electrocardiograms are displayed as blue, while signals recorded from the 36 posterior electrocardiograms are green. Abbreviations; CRT, Cardiac resynchronization therapy; LBBB, Left bundle branch block.

Implementation of the ECG belt during CRT device optimization

Improvements in wavefront fusion and cancellation with atrioventricular delay optimization during simultaneous biventricular pacing (Figure 3), and interventricular delay optimization during sequential biventricular pacing (Figure 4), were assessed using this investigational ECG belt. The effect of optimizing the atrioventricular delay during atrial-synchronized LV-only pacing with corresponding improvements in ventricular fusion was additionally measured (Figure 5).

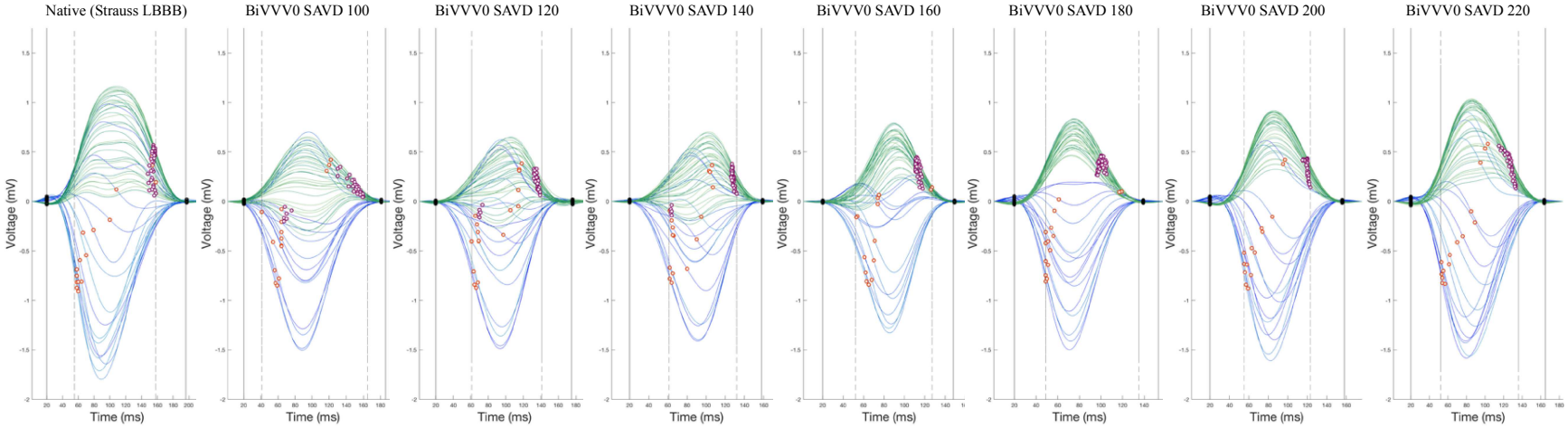

Figure 3. *Ventricular activation during native (Strauss LBBB) conduction, and simultaneous biventricular pacing at atrioventricular delays ranging from 100 to 220 milliseconds*

Native Strauss LBBB conduction was characterized by a unidirectional wavefront that traversed posteriorly, demonstrated via positive and negative deflections in the posterior and anterior electrocardiograms, respectively. Data was acquired during simultaneous biventricular pacing at atrioventricular delays that ranged from 100 milliseconds to 220 milliseconds, and in 20 millisecond increments. Biventricular pacing represented ventricular fusion from three wavefronts: a rightward and anteriorly-moving LV paced wavefront, a leftward and posteriorly-moving RV paced wavefront, and a posteriorly-moving native wavefront. Improved electrical synchrony with biventricular pacing was evidenced by reduced durations and peak amplitudes of the electrocardiograms. There were minimal morphological changes in the ventricular fusion complexes with incremental lengthening of the atrioventricular delay. Furthermore, the peak amplitudes of the negative anterior electrocardiograms were consistently and disproportionately greater than that of the peak amplitudes of the positive posterior electrocardiograms. This morphology of the electrograms represents that the leftward and posteriorly-moving native and RV paced wavefront persistently, and irrespective of the atrioventricular delay, exerted a greater contribution to ventricular fusion than the LV paced wavefront. Abbreviations: BiVVV0, Simultaneous biventricular pacing; LBBB, Left bundle branch block; SAVD, Sensed atrioventricular delay.

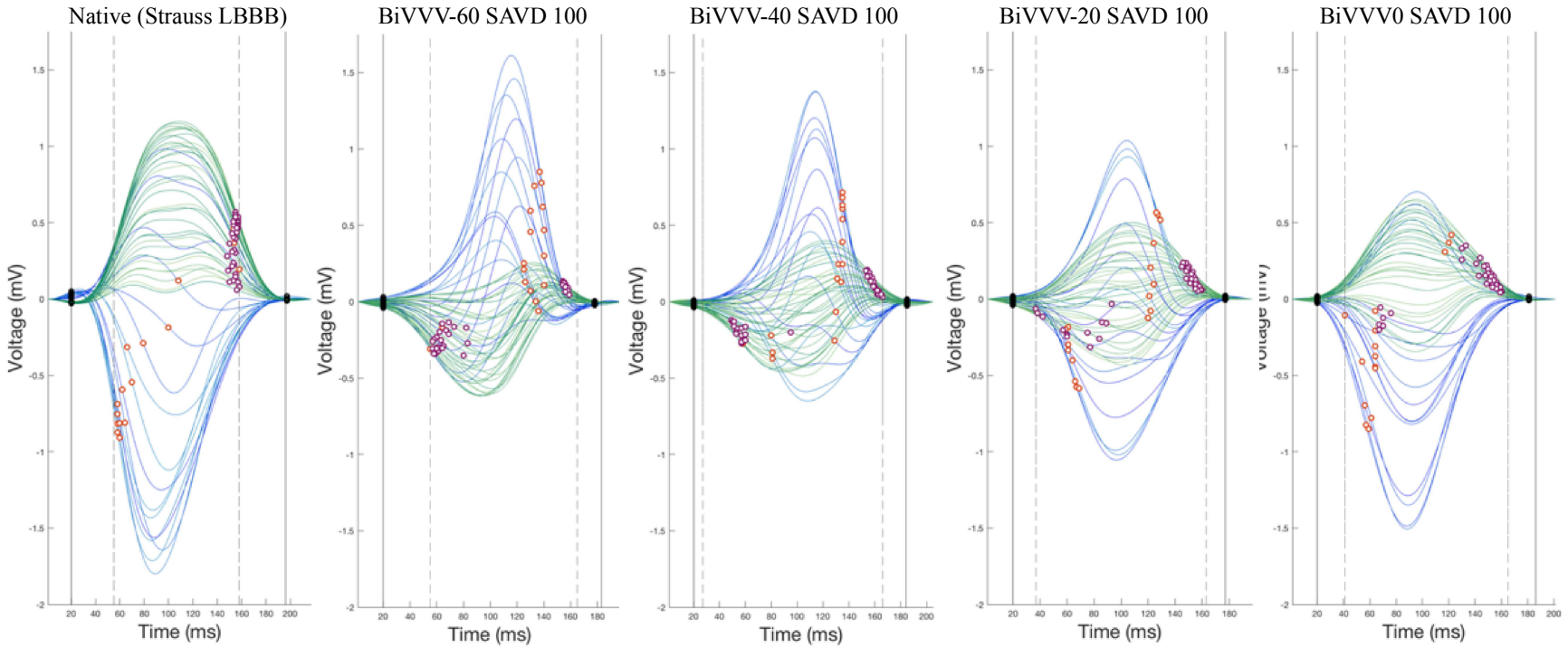

Figure 4. *Ventricular activation during native (Strauss LBBB) conduction, and sequential biventricular pacing with LV preactivation ranging from 20 to 60 milliseconds at a sensed atrioventricular delay of 100 milliseconds*

Electrocardiographic data was acquired with sequential biventricular pacing, specifically during LV preactivation up to 60 milliseconds. Negative interventricular delays indicate LV preactivation; BiVVV-20, BiVVV-40, and BiVVV-60 represent LV preactivation durations of 20, 40, and 60 milliseconds, respectively. The anterior electrodes increased in amplitude and became progressively positively deflected with greater LV preactivation. The posterior electrocardiograms concurrently reversed in polarity, and were predominately negatively deflected with greater LV preactivation. The peak amplitudes of the positively deflected anterior electrograms disproportionally surpassed that of the peak amplitudes of the posterior electrocardiograms at the greatest interventricular delay of 60 milliseconds. This represented that the anteriorly-moving LV paced wavefront exerted a greater contribution to ventricular fusion, and was associated with minimal contribution from the posteriorly-moving native and RV paced wavefronts. Abbreviations: BiVVV0, Simultaneous biventricular pacing; LBBB, Left bundle branch block; SAVD, Sensed atrioventricular delay.

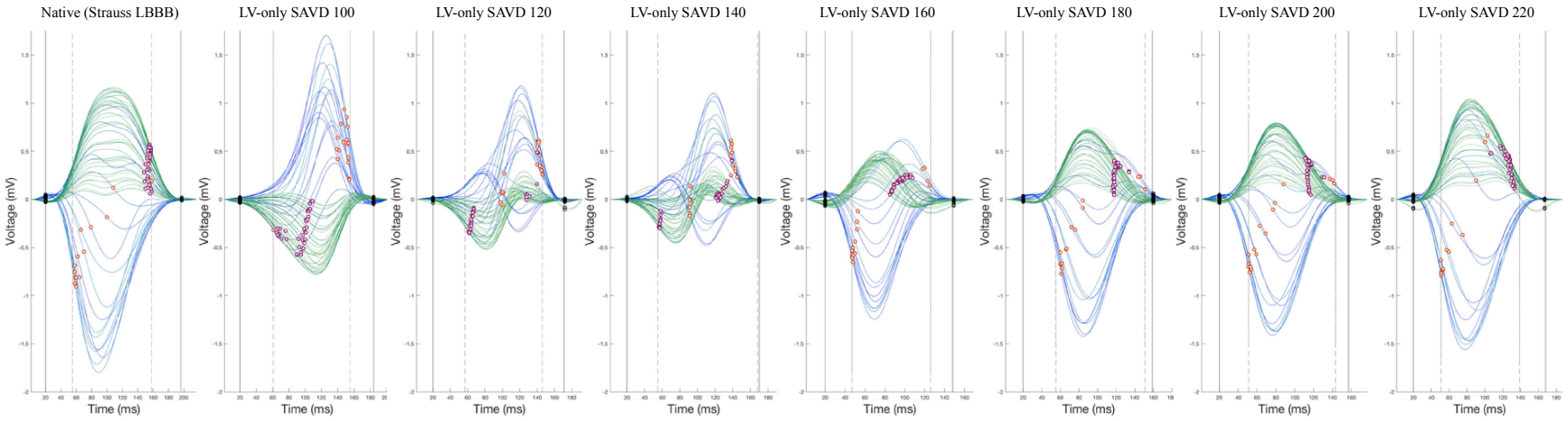

Figure 5. *Ventricular activation during native (Strauss LBBB) conduction, and atrial-synchronized LV-only pacing with atrioventricular delays ranging from 100 to 220 milliseconds*

Electrocardiographic data was acquired with atrial-synchronized LV-only pacing at atrioventricular delays that ranged from 100 milliseconds to 220 milliseconds, and in 20 millisecond increments. Atrial-synchronized LV-only pacing was composed of fusion between two wavefronts, namely the combination of the native wavefront from the intact atrioventricular node and right bundle branch that moved posteriorly, and the anteriorly-moving LV paced wavefront. At the shortest atrioventricular delay of 100 milliseconds, the anterior electrocardiograms were positively deflected, and the posterior electrodes were negatively deflected. The peak amplitude of the anterior electrodes was disproportionately larger than the peak amplitude of the posterior electrocardiograms, suggestive that the anteriorly-moving LV paced wavefront preceded the native wavefront and exerted a greater contribution to ventricular fusion. Conversely, at the longest atrioventricular of 220 milliseconds, ventricular activation predominately resembled native LBBB conduction, demonstrating that the native wavefront preceded and depolarized the ventricular myocardium prior to the LV paced wavefront. At an intermediate atrioventricular delay of 140 milliseconds, improved electrical synchrony and wavefront cancellation was evidenced by reduced durations of the ventricular fusion complexes, reduced amplitude of the electrocardiogram peak height, and reversed polarity in the anterior and posterior electrocardiograms as compared to native conduction. Abbreviations: LBBB, Left bundle branch block; LV, Left ventricle; SAVD, Sensed atrioventricular delay.

METHODS AND METRICS IN THE CHARACTERIZATION OF VENTRICULAR ACTIVATION

Adoption of ECG belt-derived area under the curve metric for device optimization

A newly proposed metric derived from ECG belt technology is area under the curve (AUC). This metric is calculated from the unipolar electrocardiograms, including the 17 anterior and 36 posterior electrodes on the upper torso (Bank et al., 2020). Proprietary software can identify QRS complexes, demarcate the steepest deflection of each electrocardiogram, and can match the 17 anterior electrocardiograms with each of the 36 posterior electrocardiograms to generate 612 pairs, and integrate the area between each pair of electrograms. The onset and end of the AUC was defined based on the earliest and latest steepest slope, respectively. The total average AUC was expressed as the average paired difference between the area under the curve, in millivolts (mV) multiplied by milliseconds (mV×milliseconds), for each anterior and every posterior ECG (i.e., the average of a 17-by-36 distance matrix) (Figure 6). The AUC is frequently negative during LBBB conduction, and characterized by a dominate native wavefront moves posteriorly. Positive AUC values typically occur during RBBB conduction, where the dominant wavefront moves anteriorly. Measurements of AUC, both during native rhythm and CRT pacing, exhibit high inter-day reproducibility (Figure 7).

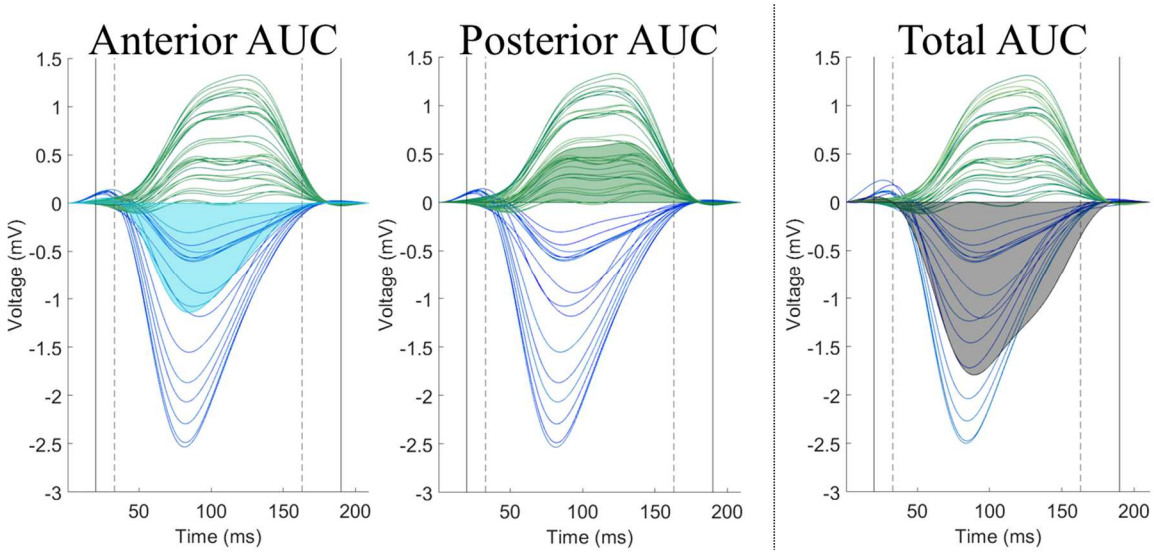

Figure 6. *Graphical representation of AUC, in voltage (millivolts) by time (milliseconds), during native LBBB conduction for anterior and posterior electrocardiograms*

The total AUC, shown in grey shading, was calculated as the paired difference between the anterior AUC (blue) and posterior (green) AUC. The total AUC was negative since the AUC for the anterior electrocardiograms was negative, and encompassed a greater area in magnitude then that of the posterior electrocardiograms. Abbreviations: AUC, Area under the curve.

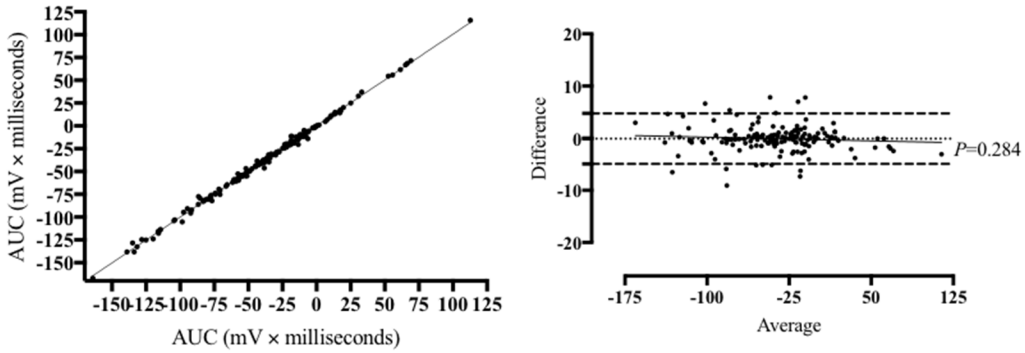

Figure 7. Reproducibility analysis of AUC (n=162 pairs)

Intra-class correlation coefficient and coefficient of variation for AUC were 0.999 and 3.8%, respectively. Repeated measurements of AUC were not significantly different (-37.2±3.5 mV×milliseconds vs. -37.2±3.5 mV×milliseconds, p=0.412). Bland-Altman plots exhibit homoscedasticity, with a non-significant trend (p=0.284). Abbreviations: AUC, Area under the curve

Effect of device optimization of the atrioventricular and interventricular delays on measures of AUC

Reductions in ventricular activation durations and peak amplitudes of the electrocardiograms, as well amelioration of dyssynchronous LBBB activation via reversed polarity within the anterior and posterior electrocardiograms, are indicative of improved wavefront fusion and cancellation. Such improvements in electrical synchrony are quantified by diminutions in the magnitude of AUC. Device optimization on corresponding measures of AUC during simultaneous biventricular pacing, sequential biventricular pacing, and atrial-synchronized LV-only pacing are presented in Figure 8, Figure 9, and Figure 10, respectively.

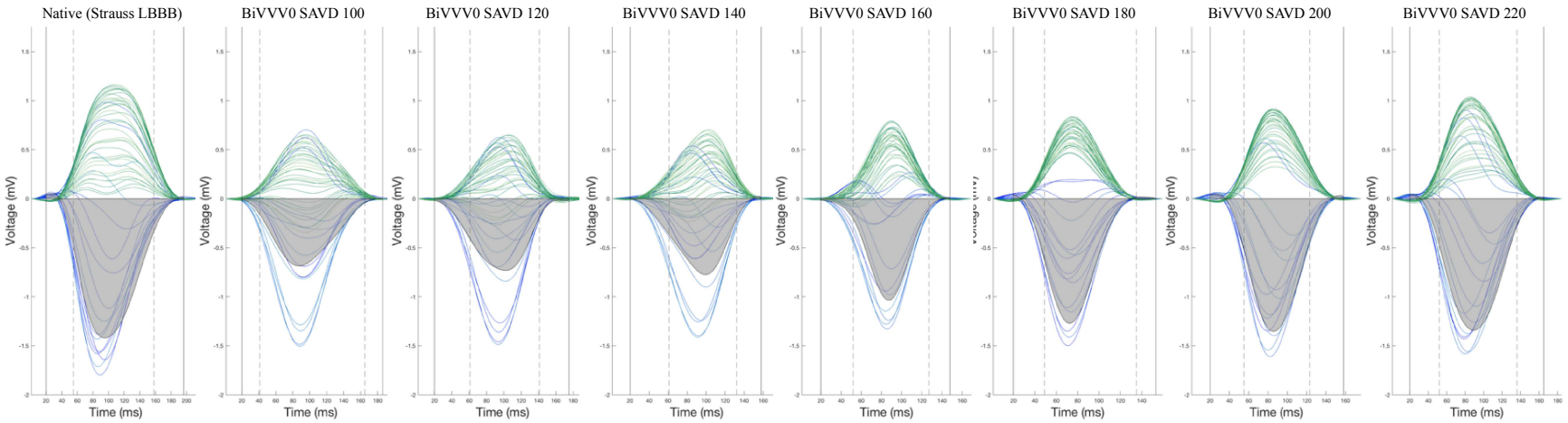

Figure 8. *Measures of AUC during native (Strauss LBBB) conduction, and simultaneous biventricular pacing at atrioventricular delays ranging from 100 to 220 milliseconds*

The AUC during native LBBB conduction was negative. Negative AUC values also occurred irrespective of optimizing the atrioventricular delay during simultaneous biventricular pacing, which indicated that the area under the negatively deflected anterior electrocardiograms was consistently greater in magnitude then that as compared to the area encompassed by the positive posterior electrocardiograms. Negative AUC with biventricular pacing represents imbalanced ventricular fusion, and occur when posteriorly-moving wavefronts from the RV lead and/or native conduction exert a greater contribution to ventricular activation than the anteriorly-moving LV paced wavefront. Further decrements in fusion between the paced ventricular wavefronts with the native wavefront were observed at prolonged atrioventricular delays (e.g., 220 milliseconds), depicted by larger amplitudes in the electrocardiograms and by increasingly negative AUC values. At prolonged atrioventricular delays, ventricular fusion largely resembled native conduction, attributable to the prevailing posteriorly-moving native wavefront that preceded and depolarized the myocardium prior to the paced ventricular wavefronts. Abbreviations: BiVVV0, Simultaneous biventricular pacing; LBBB, Left bundle branch block; SAVD, Sensed atrioventricular delay.

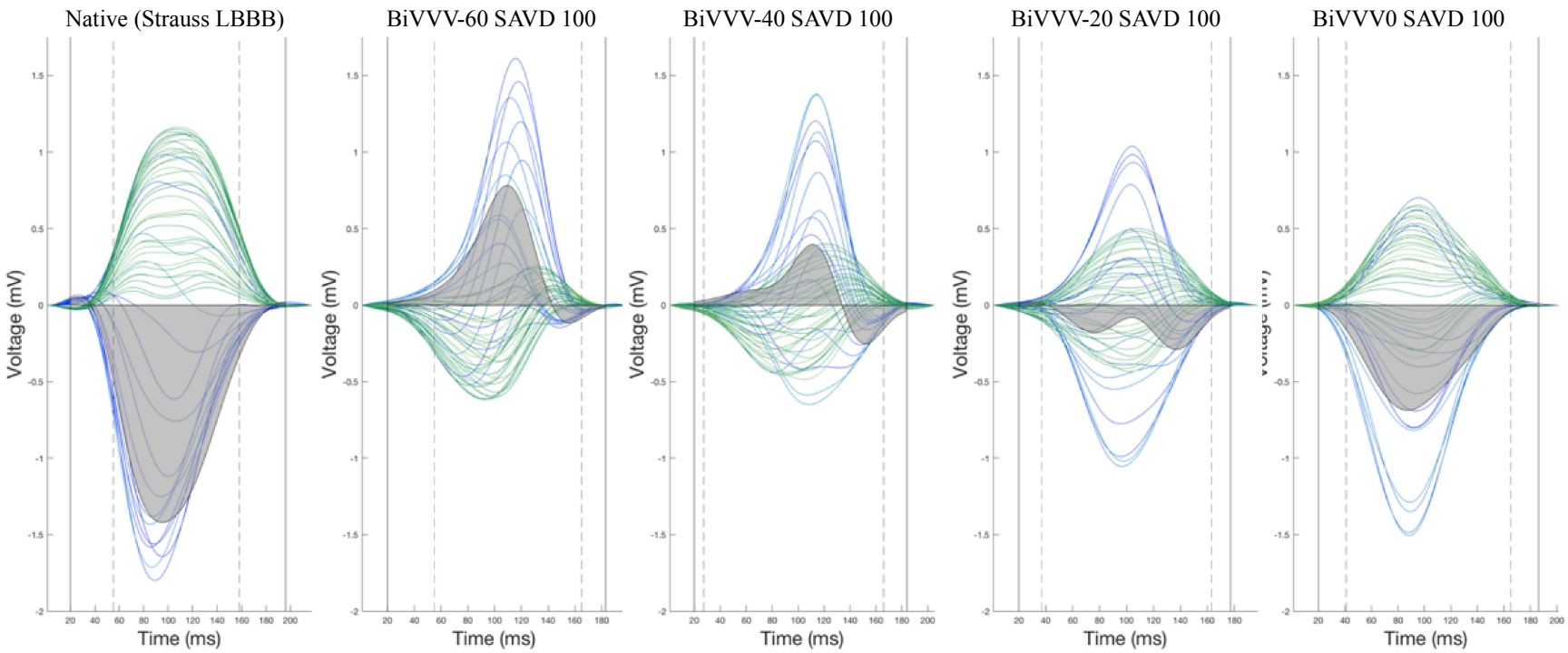

Figure 9. *Measures of AUC during native (Strauss LBBB) conduction, and sequential biventricular pacing with LV preactivation at a sensed atrioventricular delay of 100 milliseconds*

Interventricular delay optimization exhibited increasingly positive AUC values concurrently with increasing LV preactivation. Positive AUC values, at an interventricular delay with 60 milliseconds of LV preactivation for example, were attributable to ventricular fusion complexes in which the area encompassed by the positive anterior electrocardiograms was greater in magnitude than that of the area under the posterior electrocardiograms. The disproportionately greater peak amplitude of the positively deflected anterior electrocardiograms were indicative of imbalanced ventricular fusion, characterized by an increasingly predominant LV paced wavefront that moved anteriorly with minimal fusion from the posteriorly-moving wavefronts. Abbreviations: BiVVV0, Simultaneous biventricular pacing; LBBB, Left bundle branch block; SAVD, Sensed atrioventricular delay.

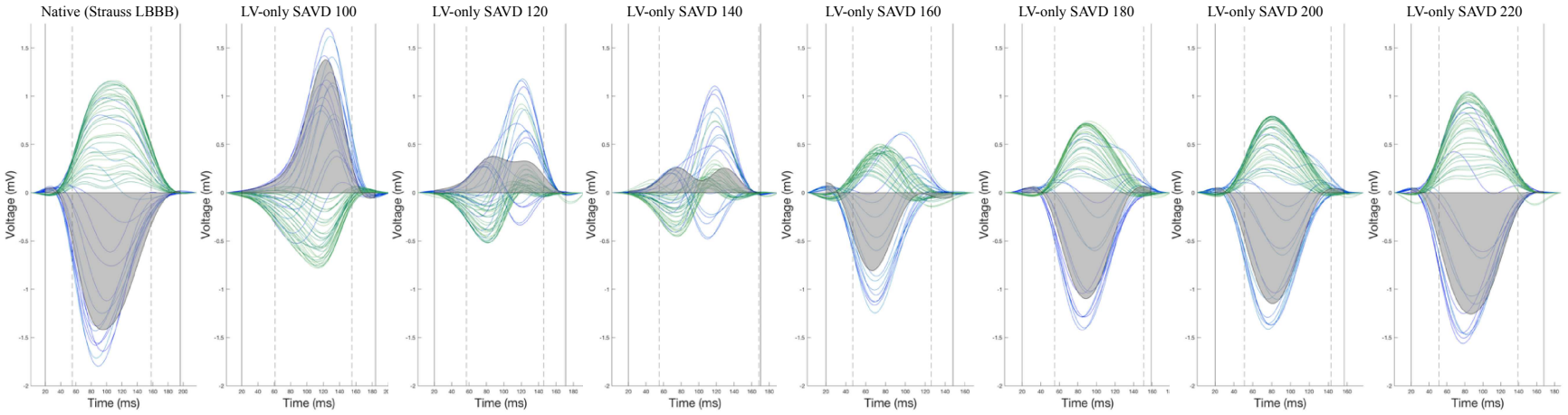

Figure 10. *Measures of AUC during native (Strauss LBBB) conduction, and atrial-synchronized LV-only pacing at atrioventricular delays ranging from 100 to 220 milliseconds*

Shorter atrioventricular delays (e.g., 100 milliseconds) with LV-only pacing correspond with positive AUC values, attributable to a dominate anteriorly-moving wavefront from the LV lead that was paced prior to the native wavefront. Measures of AUC became progressively less positive and decreased in magnitude with concurrent prolongations in the atrioventricular delay, attributable to improved timing with fusion between the LV paced wavefront and the native wavefront. After reaching an intermediate atrioventricular delay of 140 milliseconds, subsequent lengthening of the atrioventricular delay caused the AUC to become negative, and progressively resembled that of native conduction. Prolonged atrioventricular delays, particularly greater than 160 milliseconds, correspond with negative AUC values, attributable to a greater contribution of the posteriorly-moving native wavefront to ventricular fusion. Abbreviations: LBBB, Left bundle branch block; LV, Left ventricle; SAVD, Sensed atrioventricular delay.

CARDIAC RESYNCHRONIZATION INDEX AS A NOVEL, PATIENT-SPECIFIC METRIC OF ELECTRICAL SYNCHRONY

Assessment of cardiac resynchronization index

The relative change in AUC at any given pacing setting normalized to native conduction, known as cardiac resynchronization index (CRI), quantified the percent improvement in electrical synchrony during CRT pacing: $([AUC_{Native} - AUC_{CRT\ pacing}]/AUC_{Native})\times100)$ (Bank et al., 2020). Displayed in Figure 11 are CRI values during biventricular pacing, both simultaneous and sequential, and atrial-synchronized LV-only pacing for the aforementioned patient presented in this case report.

Simultaneous biventricular pacing corresponded with a range of CRI values between 59.7% at the best atrioventricular delay of 120 milliseconds, to 19.7% at an atrioventricular delay of 220 milliseconds. Optimizing the atrioventricular delay between 100 to 180 milliseconds elicited trivial changes in CRI values that specifically ranged between 49.4% to 59.7%. Decrements in electrical resynchronization at prolonged atrioventricular delays greater than 200 milliseconds were attributable to a greater contribution of the native wavefront to ventricular fusion.

Optimal electrical synchrony occurred with LV preactivation of 20 milliseconds, as measured by a CRI value of 82.7%. In comparison, simultaneous biventricular pacing at the same atrioventricular delay of 100 milliseconds had a CRI of 49.4%. Decrements in percent electrical resynchronization occurred with subsequent LV preactivation past the optimum interventricular offset, as characterized by imbalanced ventricular activation from a greater contribution of the anteriorly-moving LV paced wavefront and minimal fusion from the RV paced wavefront.

Atrial-synchronized LV-only pacing exhibited a peak electrical resynchronization value of 82.1% at an intermediate atrioventricular delay of 140 milliseconds. The LV wavefront preceded the native wavefront at shorter atrioventricular; specifically, at atrioventricular delays that were either 140 milliseconds or shorter. At atrioventricular delays that were at least 160 milliseconds in duration, the native wavefront depolarized the myocardium prior to the LV paced wavefront.

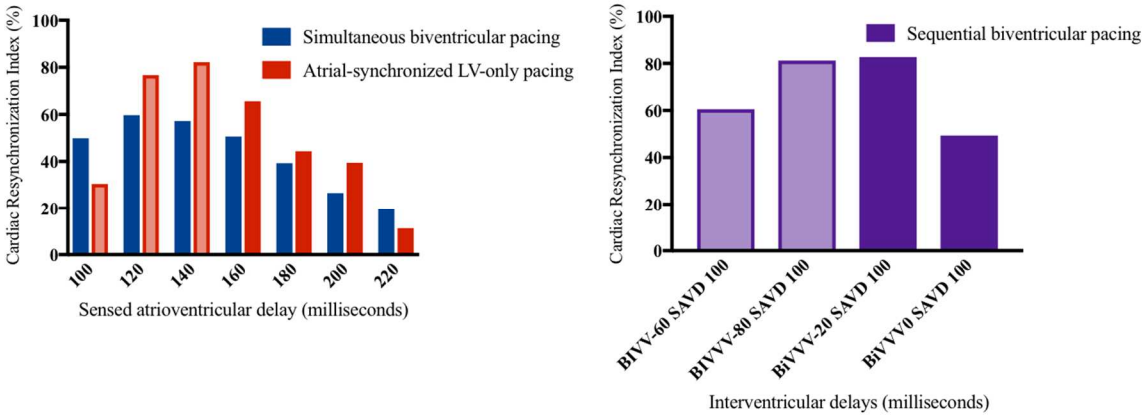

Figure 11. *Percent electrical resynchronization during CRT pacing*

Red colors correspond to CRI during atrial-synchronized LV-only pacing. Blue and purple colors represent CRI during simultaneous and sequential biventricular pacing, respectively. Positive AUC values, which represent a dominate LV paced wavefront that preceded the native and/or RV paced wavefront, were indicated with light shading. Negative AUC values were represented with darker shading. Abbreviations; LV, Left ventricular; SAVD, sensed atrioventricular delay.

ELECTRICAL DYSSYNCHRONY MAPPING

Systematic characterization of the potential for electrical resynchronization during simultaneous and sequential biventricular pacing

The electrical potential for resynchronization during CRT pacing can be individually visualized for a patient as a three-dimensional surface plot by acquiring CRI during simultaneous and sequential biventricular pacing at various atrioventricular delays (Figure 12). The duration, in milliseconds, that spanned when the LV lead was paced following sensing an intrinsic, or paced, atrial contraction (i.e., A-LV interval) is the horizontal axis. The duration, in milliseconds, that spanned between when the RV lead was paced following sensing an intrinsic, or paced, atrial contraction (i.e., A-RV interval) is the vertical axis. Simultaneous biventricular pacing corresponds to the diagonal line that extended from the bottom left corner to the top right corner of the matrix. Pacing settings to the left of the diagonal line represent sequential biventricular pacing with LV preactivation. Intuitively, pacing settings right of the diagonal line of simultaneous pacing reflect sequential biventricular pacing with RV preactivation. Matrices are then overlaid with a cubic spline interpolation; red colors indicate CRI values greater than 80% electrical resynchronization, and dark blue colors represent CRI values less than 20%.

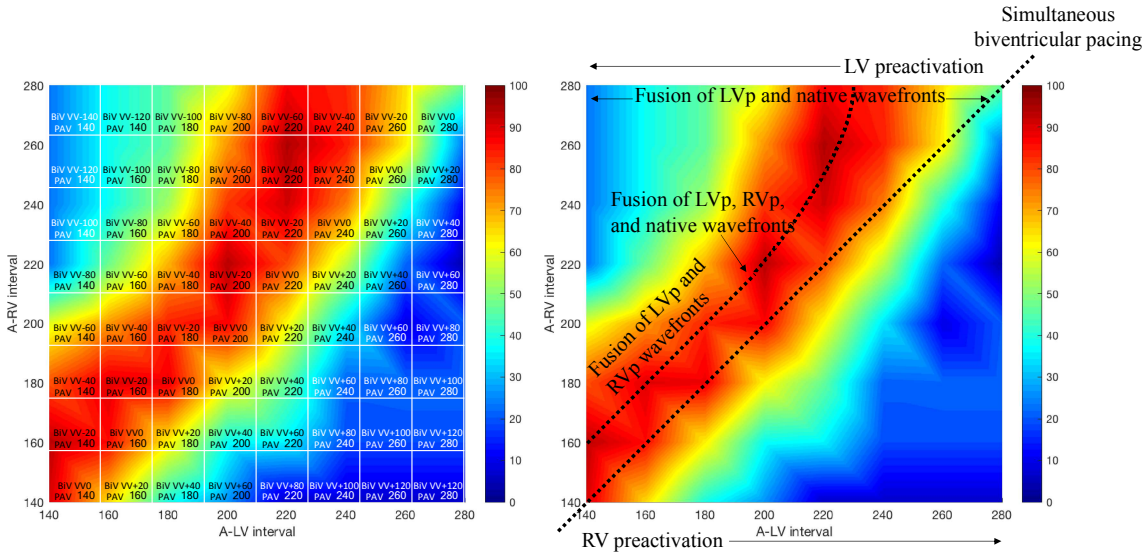

Figure 12. *Electrical dyssynchrony matrix for a Medtronic CRT device*

The patient had an underlying Strauss LBBB conduction (QRSd 182 milliseconds) with a first degree AV block (PR interval: 222 milliseconds). Abbreviations: A-LV, Atrial-Left ventricular paced; A-RV, Atrial-Right ventricular paced; LV, left ventricular; LVp, Left ventricular paced; PAVD, Paced atrioventricular delay; RV, Right ventricular; RVp, right ventricular paced.

Effect of native QRS morphology on the corresponding therapeutic potential for electrical resynchronization

Electrical dyssynchrony mapping with native 12-lead ECGs for Strauss LBBB and IVCD QRS morphology are presented in Figure 13. Both patients had a Medtronic CRT pacemaker or defibrillator. The patient with Strauss LBBB conduction was a 57 year-old male that had a QRSd of 160 milliseconds and a PR interval of 200 milliseconds; the atrial-sensed to RV-sensed (AsRVs) interval was 200 milliseconds. The patient with IVCD conduction was a 72 year-old female with a QRSd of 120 milliseconds and a PR interval of 160 milliseconds; the AsRVs interval was 150 milliseconds. Both patients had data acquired at

sensed atrioventricular delays (i.e., A-LV interval) ranging from 40 milliseconds to 200 milliseconds, and with interventricular delays (i.e., A-RV interval) from 20 milliseconds of RV preactivation to 80 milliseconds of LV preactivation. Atrioventricular and interventricular delays were also acquired in 20 millisecond increments.

Both LBBB and IVCD conduction electrically respond to CRT pacing via a similar continuous ridge of optimum electrical synchrony, and exhibit a leftward turn concurrent with incremental increases in the atrioventricular delay. During short A-LV intervals, simulated via programming the atrioventricular delays for Medtronic CRT devices, the ridge of optimum pacing was predominately parallel to the diagonal line of simultaneous biventricular pacing. This was reflective of fusion between the two paced ventricular wavefronts, and without native contribution. As the atrioventricular delay lengthened, increased contribution of the native wavefront fused with the paced ventricular wavefronts. The onset of the leftward turn in the ridge of optimum electrical synchrony indicated the beginning of triple wavefront fusion, which was composed of native conduction fusing with the two paced ventricular wavefronts. The ridge of optimum pacing becomes vertical and parallel to the A-RV axis with subsequent lengthening of the A-RV interval. At these pacing configurations, ventricular activation predominately consisted of fusion between the LV-paced wavefront with the native, and with minimal fusion from the RV paced wavefront. Additionally, pacing settings that correspond with optimal electrical synchrony predominately occurred during sequential pacing with LV preactivation for both LBBB and IVCD QRS morphologies.

Unlike LBBB and IVCD conduction, patients with high-grade atrioventricular block have no native conduction to fuse with the paced ventricular wavefronts. The persistent lack of fusion with the native wavefront is supported by the observation that the ridge of optimum electrical resynchronization was consistently parallel to the line of simultaneous biventricular pacing across all atrioventricular delays (Figure 14). Additionally, similar to IVCD and LBBB conduction, patients with high-grade atrioventricular block exhibit a continuous ridge of optimal electrical synchrony during pacing configurations that correspond with LV preactivation.

CONCLUSIONS AND CLINICAL APPLICATIONS

The data presented in this supplemental appendix provided a patient-specific example in quantifying the relative improvements in electrical synchrony across different pacing configurations, including biventricular and atrial synchronized LV-only pacing. Also disclosed in this appendix was a methodology that systematically evaluated the therapeutic potential for electrical resynchronization during simultaneous and sequential biventricular pacing. Cardiac resynchronization index provides an individualized assessment of electrical dysssynchrony during native rhythm, and shows promise in quantifying the potential for wavefront fusion and cancellation during CRT pacing. It has widespread applicability to be a component of standard care for CRT patients in the future, owning to it non-invasive, efficient, practical, and inexpensive attributes.

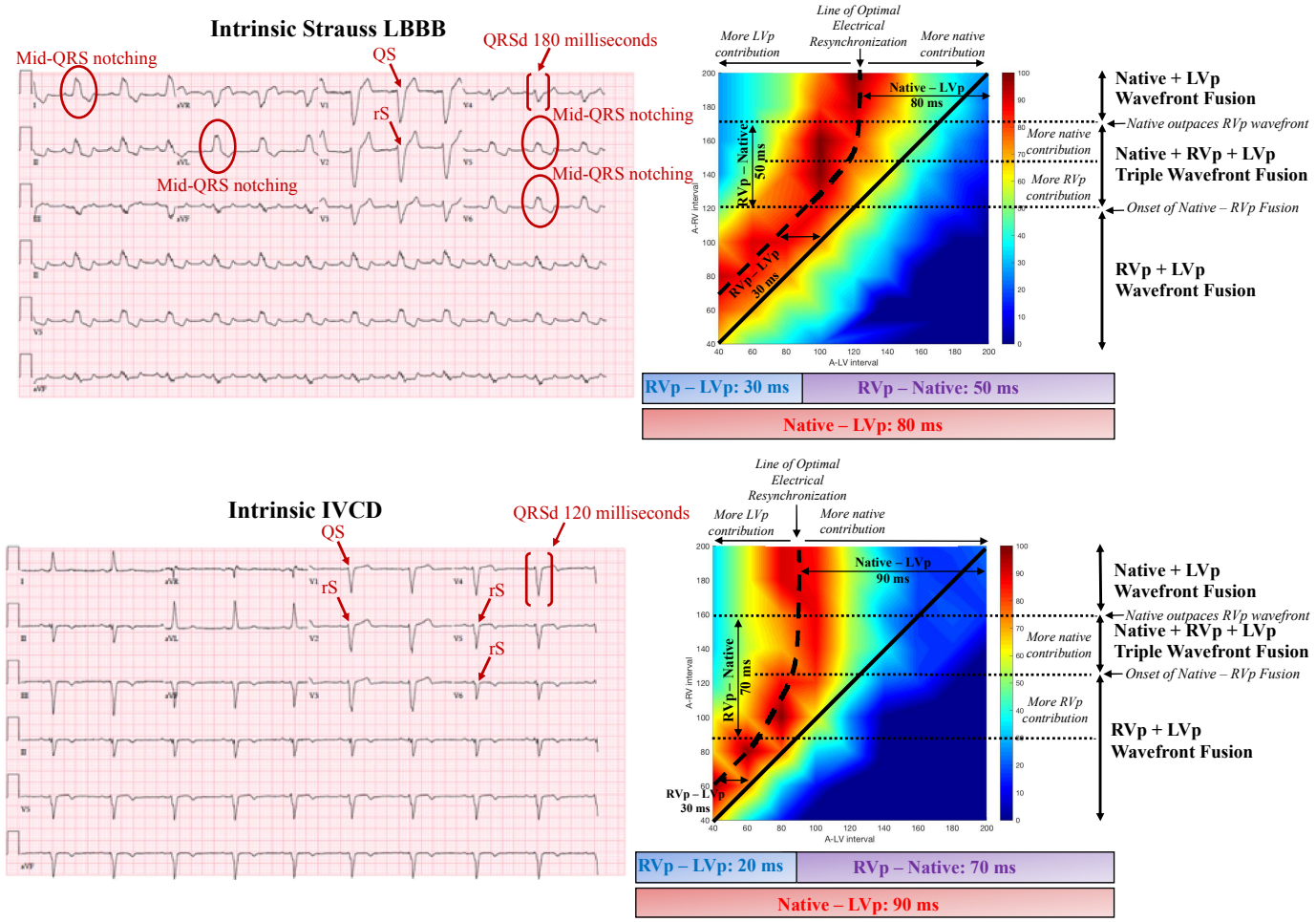

Figure 13. *Strauss LBBB and IVCD QRS morphology with corresponding electrical dyssynchrony mapping.*

Abbreviations: IVCD, Interventricular conduction delay; LBBB, Left bundle branch block; LVp, Left ventricular paced, QRSd, QRS duration, RVp, Right ventricular paced.

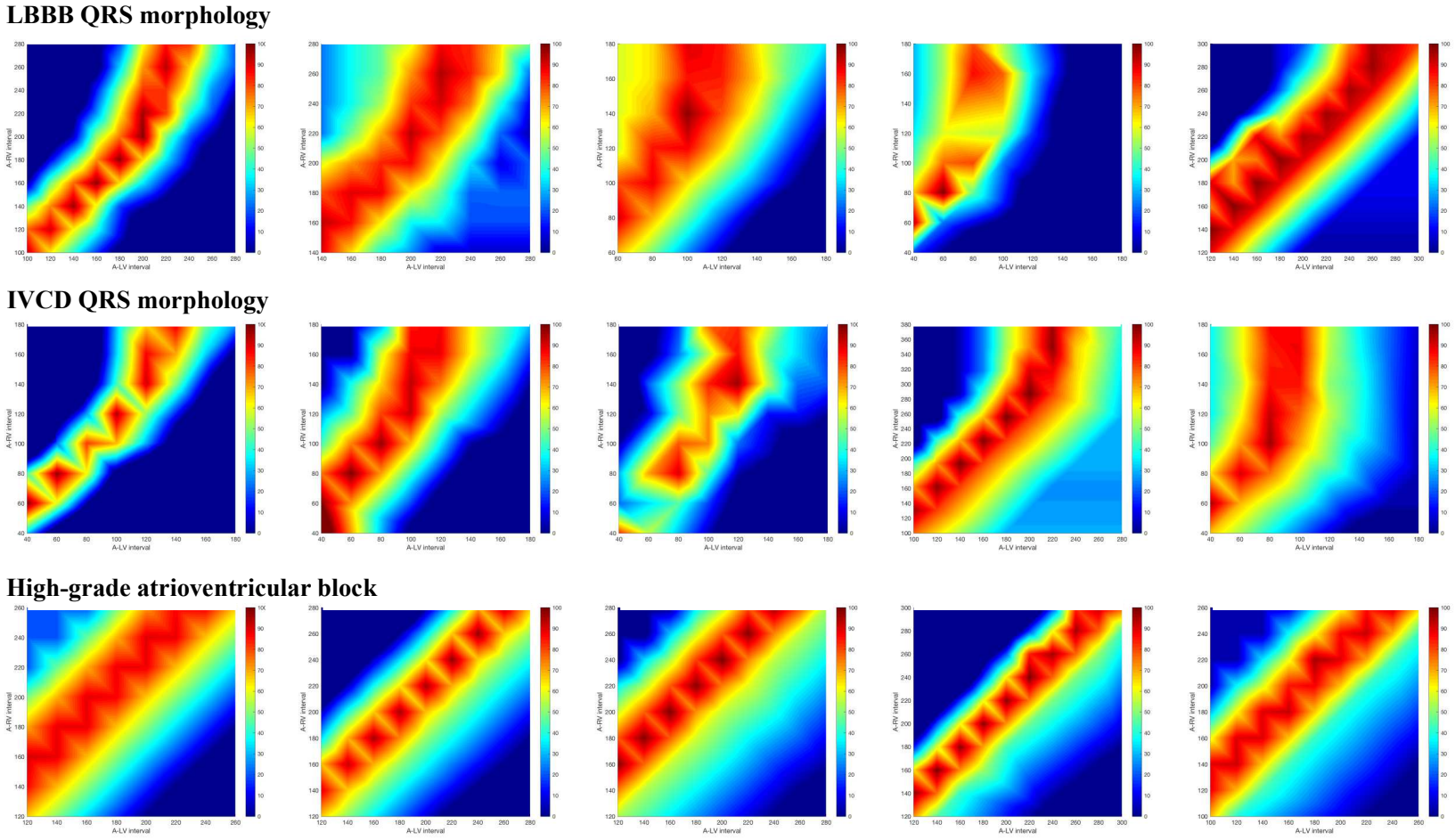

Figure 14. *Electrical dyssynchrony mapping for patients with LBBB (n=5), IVCD (n=5), and RV-paced rhythm (high-grade AV block; n=5)*

Right ventricular paced rhythm was used in placed of native rhythm for patients with high-grade atrioventricular block. Abbreviations: A-LV, Atrial-LV; A-RV, Atrial-RV; IVCD, Interventricular conduction delay; LBBB, Left bundle branch block.